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Editorial

Management of the nephrotic syndrome

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The use of corticosteroids has brought radical changes in the management of the nephrotic syndrome in the past 10 years. The physician who pushes these preparations diligently may expect diuresis in as high as 90 per cent of the victims of nephrosis and may expect the majority to have a substantial reduction in albuminuria. In roughly 10 per cent of the patients the urine will become free of albumin and remain so after a 10 to 12-day course of corticosteroids. There is no evidence at present, and no evidence can be expected from the therapy of patients, that treatment alters the underlying tendency for the disease to return. The course of the nephrotic syndrome is so variable, and the treatment varies so much from patient to patient that it seems unlikely that any physician can even hope to learn the answer to this question. There *is* general agreement that we are keeping patients from dying from renal failure.

This is a serious disease with a 3-year mortality rate of about 30 per cent and a 4-year mortality rate of roughly 40 per cent in the 500 cases reported by Riley.[1] Some of these patients had been treated sporadically for the elimination of edema only. Since the present treatment with corticosteroids was begun, the 3 to 4-year mortality rate has been reduced in some small series to 0-8 per cent. Treatment has varied so much from group to group that the true mortality rate is difficult to ascertain, but no authority seems to question that, at least, death has been deferred.

Complications of prolonged therapy constitute a serious objection. Daily continuous administration in high dosage may cause loss of protein matrix, with collapse of one or more vertebral bodies. This happened to one of our earlier patients. Bilateral cataracts, with loss of all but the perception of light, has been observed by the author, and less complete lenticular opacities have been reported by others.[2] Short-term high dosage (400 to 1,000 mg. of cortisone) therapy has been accompanied by symmetrical bilateral aseptic necrosis of the femoral heads[3] in patients who were being treated for dermatological conditions. The author has had a patient on low-dosage therapy (4 to 6 mg. of methylprednisone for most of the time) for 9 years for disseminated lupus. This patient developed bilateral aseptic necrosis of the femoral heads after 6 years, which was thought to be caused by her lupus. After 8 years, bilateral aseptic necrosis of the mandibular condyles occurred. No other such case has been reported, but the symmetry is so striking that the resemblance to the high-dosage cases cannot be denied, although lupus alone can do the

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same thing. The other complications are more common and familiar: Cushing's disease, susceptibility to infection, especially breakdown of tuberculosis and perhaps dissemination of varicella, masking of pain and signs of infection, duodenal ulcer, acne and other less serious phenomena. Hypertension occurs more frequently during the treatment of the nephrotic syndrome than during that of most other conditions and may become a seriously limiting factor to treatment. Awareness of these complications often suggests remedies for them. Fortunately, aseptic necrosis and extensive formation of cataracts are infrequent, although minor cataracts are fairly common.

Since plans of treatment are varied and general agreement has not yet been reached as to which is best, it may be well to summarize a statement by Conrad Riley[4] with which all members of the National Nephrosis Foundation were in agreement: (1) Corticosteroids should be given in large dosage as quickly as a diagnosis of nephrosis is made. (2) The preparation to be used seems to depend on personal preference. (3) Initial treatment should be continued for a long time, long enough to return the patient, if possible, to a relatively normal state with regard to all the available measurements. (4) After the initial treatment, some long-term plan should be made for either re-treatment or continued treatment. Some give steroids continuously, gradually reducing the dose; others wait for signs of relapse. (5) All agree that proteinuria and not edema should be the determining factor in the decision to resume treatment.

The choice of steroids, as mentioned above, is a personal matter. Lange[5] treated 60 nephrotic patients with triamcinolone and was impressed with the improvement in response over results with cortisone in the same patient. Two of his patients experienced marked weakness of the quadriceps muscles and of other leg muscles. This persisted long after therapy was discontinued and has persuaded him to abandon triamcinolone in the prolonged continuous treatment of nephrotic patients.

Daily treatment produces quicker improvement[6] but treatment with twice the dose on 3 consecutive days each week is safer. Therefore, most authorities prefer to give either 5 weeks of continuous therapy or continuous therapy until the urine has been albumin-free for at least 2 weeks, whichever is the shorter period. Steroids are then withdrawn, and if the patient relapses he is placed on corticosteroids for 3 consecutive days a week. Believing that the smaller the amount of corticosteroids used the better, the author always tries a 12-day course of therapy, and, if the patient's urine becomes free of albumin and remains so, no further treatment is given. This has occurred in about 10 per cent of the patients in some series. If relapse occurs, 3 to 5 weeks of daily therapy are given, and then the patient is switched to administration of the steroid for 3 consecutive days a week with twice the dose. Lange arbitrarily continues this for a year. Heymann[7] continues for 2 to 7 months, depending upon the response of the patient. Our practice has been to cut the dose in half after a month of albumin-free urine, cut this in half after another month, and discontinue usage after another month. In some patients, we have maintained the same dose but dropped administration of it to 2 days a week for a month, then 1 day, then off. Lange, at one time, used the latter method and believed that it was the better one. The author has had too few cases to be able to judge. Many relapses occur with either method. Relapses require a trial first of 3-day therapy, but, if the condition is severe or if the patient does not respond, a return to daily therapy may be necessary. If there is no response after the first 5 weeks of daily treatment the patient is usually changed to 3-day therapy anyway. Response should be judged by the quantitative 24-hour excretion of albumin.

Dosage

Dosage is varied rather arbitrarily. Five tablets (4-mg. tablets of methylprednisone; 25-mg. tablets of cortisone) for younger children, up to twelve tablets a day for adults in the 3-day treatment, and one half to three fourths as much in the daily treatment are employed. Our patients or their parents are taught to check the patient's urine for albumin daily, and they continue to do so until the urine has been free of albumin for a year. This creates a certain amount of anxiety but also allays a

great amount. It has the advantage of bringing the patient back to the doctor promptly if relapse occurs.

Luetscher[8] has pointed out the advantage of checking the blood sodium of the severely edematous subject prior to treatment and suggests giving salt-poor albumin if the sodium is low. A water diuresis results from this, bringing the sodium level up to normal. If this is not done, the administration of corticosteroids may precipitate cerebral edema and convulsions. We have not seen this with any preparations other than ACTH, but it has been reported.

Infections and antibiotics

There is some disagreement about cessation of treatment during infections. Metcoff[9] believes that he has seen fewer serious reactions with cessation of therapy. Cooke, Lange, Heymann and Guild[10] do not stop therapy, and it has often been our practice to increase the dose during infections. Most authorities agree that therapy should be continued if the infecting organism can be adequately covered with an antibiotic, but many are uncertain about what to do in the case of infections which cannot be covered, particularly infections which may possibly be aggravated by corticosteroids, such as varicella. The author has carried 2 patients through varicella on steroids without mishap, but this not mean that it can always be done.

Heymann[7] gives routine antistreptococcal prophylaxis in the form of Gantrisin. No one is really sure that this helps, and most prefer to treat the infection when it occurs, if recognized. No controlled series has been reported on this subject.

The complicated case

The patient who develops serious hypertension or who has a precipitous rise in nonprotein nitrogen presents a special problem. Once diuresis is established, the blood pressure and nonprotein nitrogen may fall rapidly, but, in cases in which diuresis is delayed, temporary cessation of treatment may be necessary. If prompt improvement in blood pressure and/or nonprotein nitrogen occurs, a compromise treatment of 1 or 2 days a week can be tried and gradually built up as tolerated. Permanent hypertension is a serious deterrent but may sometimes be controlled with drug therapy, especially hydralazine.

Collateral therapy

Chlorothiazide and other diuretics are useful in some patients but do not prevent albuminuria and renal failure. Salt-poor albumin does not affect the renal lesion but may be a helpful adjunct in the severely edematous subject. Nitrogen mustards are seldom mentioned now and seem to add little to corticosteroid therapy. Guild[10] and a few others believe that gamma globulin given once or twice a month reduces the number of infections. Others believe that infections other than coccal ones occur no more frequently than in the normal population. No one seems to have had a controlled series treated with gamma globulin.

A low-sodium diet with potassium supplement may be needed when the larger doses are being administered, even with the newer preparations. This is particularly true if chlorothiazide or another saluretic agent is being employed.

Bed rest is a useful adjunct in rendering the patient free of edema initially and may be resorted to in the more severe relapses. It is more difficult to keep the urine free of albumin if the subject is ambulatory, but the improved morale and the practical value of the ambulatory state seems to us to outweigh this disadvantage. We advise against competitive sports for 6 months after the urine clears and then suggest a gradual increase in activities controlled by daily urine tests.

Spirolactone[11] failed to eliminate edema in 4 patients reported by Milton Rapoport.

Prognosis of the aggressively treated patient as compared to the patient who has received no treatment at all is difficult to ascertain since historical controls cannot safely be matched with patients being treated currently. No investigator seems willing at the present time to alternate cases, and it is doubtful whether any subject or his parents would permit any patient to be used as a control regardless of the physician's wishes. Riley's data[12] indicate that the 5-year survival rate of patients whose disease began in the pre-steroid era, but after the advent of antibiotic therapy, is roughly 20 per cent less than the survival rate of patients who acquired the disease

in 1952 or later. This suggests, and most investigators agree, that we are prolonging life, but there are still insufficient data to say that we are changing the eventual outcome. Few seem to question the fact that corticosteroids have diminished the morbidity and improved the ability of the average patient to live a more normal life than before. Lange has treated his patients more intensively and consistently than any other group has been treated, and eventually a detailed analysis of his cases may be rewarding, including a report on those patients discontinuing and excluded from treatment.

REFERENCES

1. Riley, C.: Proceedings of the Sixth Annual Conference on the Nephrotic Syndrome, 1954, p. 260.
2. Black, R. L., and Oglesby, R. B.: Subcapsular cataracts induced by corticosteroids, J.A.M.A. **174**:166, 1960.
3. Heimann, W. G., and Freiberger, R. H.: Avascular necrosis of the femoral and humeral heads after high-dosage corticosteroid therapy, New England J. Med. **263**:672, 1960.
4. Riley, C.: Proceedings of the Eleventh Annual Conference on the Nephrotic Syndrome, 1960, p. 284.
5. Lange, K.: Proceedings of the Eleventh Annual Conference on the Nephrotic Syndrome, 1960, p. 288.
6. Merrill, A. J.: The nephrotic syndrome, Am. Heart J. **53**:305, 1957.
7. Heymann, W.: Proceedings of the Eleventh Annual Conference on the Nephrotic Syndrome, 1960, p. 289.
8. Luetscher, J. A., and Mulrow, P. A.: The nephrotic syndrome, Disease-a-Month, August, 1956.
9. Metcoff, J.: Proceedings of the Eleventh Annual Conference on the Nephrotic Syndrome, 1960, p. 292.
10. Cooke, R., Lange, K., Heymann, W., and Guild, H.: Proceedings of the Eleventh Annual Conference on the Nephrotic Syndrome, pp. 292, 293.
11. Rapoport, M.: Proceedings of the Eleventh Annual Conference on the Nephrotic Syndrome, p. 286.
12. Riley, C.: Proceedings of the Tenth Annual Conference on the Nephrotic Syndrome, 1959, p. 173.

Clinical communications

Silent mitral incompetence

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The presence of an apical systolic murmur has long been recognized as a prerequisite for the diagnosis of mitral incompetence. So important, in fact, is this physical sign that mitral incompetence is frequently diagnosed on the basis of murmur alone. According to Brigden and Leatham,[1] Hope (1849) was the first to relate the presence of a mitral systolic murmur to mitral regurgitation, and for the rest of the nineteenth century, with the exception of Potain, apical systolic murmurs were regarded as organic and attributed to mitral incompetence. The influence of Graham Steell[2] and Sir James MacKenzie,[3] followed by Lewis[4] and more recently Evans,[5] led to a break with this traditional view, with the result that the mitral systolic murmur was relegated to insignificance. The pendulum had swung too far, however. Sprague and White,[6] Boone and Levine,[7] Fishberg,[8] and Master[9] were among those who felt that a mitral systolic murmur could not be regarded as innocent and insignificant, and with the advent of cardiac surgery this view has been justified.

Gross organic mitral incompetence is readily diagnosed by the almost invariable presence of a loud apical pansystolic murmur. Greatly reduced cardiac output from uncontrolled cardiac failure or arrhythmia may soften the murmur, but in the absence of such factors it is not sufficiently appreciated that gross mitral incompetence may be murmurless. Thus, although the interpretation of a systolic murmur at the apex may at times be debatable, it is generally held that the diagnosis of mitral incompetence is very seldom tenable or even worth considering in the absence of a murmur.

We report here the occurrence of silent mitral incompetence. The absence of any murmur, systolic or diastolic, in all but one of the six cases resulted in failure to consider valvular heart disease in the differential diagnosis at the bedside. However, the salient clue in all was disproportionate left atrial enlargement, which led to the appropriate investigations and the correct diagnosis of gross but silent mitral incompetence. It seemed worth while to draw attention to this situation, since mitral incompetence may well be correctable by surgical methods, and the absence of murmurs may lead to the diagnosis of myocardiopathy of unknown origin.

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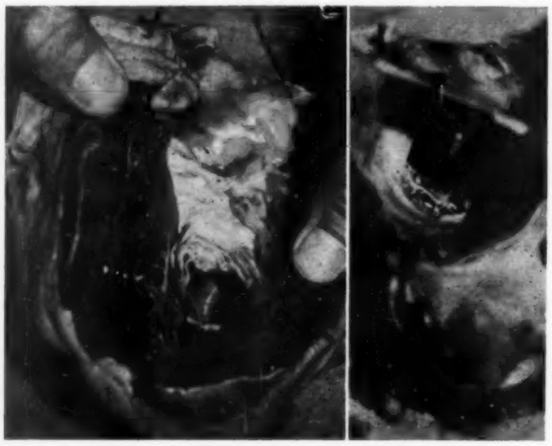

Fig. *1*. Appearance of the mitral valves from the left ventricle and left atrium; both chambers are hypertrophied and dilated. The valve ring is dilated, and gross mitral incompetence is present. The valves are sclerosed and the chordae are thickened, fused, and shortened with fibrosis of the papillary muscles.

Case reports

Case 1. G. C., a 70-year-old white woman, was first seen in August, 1951, with a history of normal health until the occurrence of an attack of acute nocturnal dyspnea 3 months before. From that time on she noticed effort dyspnea, which was progressive until she began to experience orthopnea and paroxysmal nocturnal and diurnal dyspnea. On examination she was found to have atrial fibrillation, moderate jugular venous distention, and a 6-cm. tender hepatomegaly. Her eyes were prominent, and the thyroid was nodular. Her blood pressure was 205/120 mm. Hg; the apex was left ventricular in type and displaced outward. An intermittent third heart sound was audible. *Repeated examination failed to elicit any murmurs.* With bed rest and digitalis, the blood pressure soon dropped to 160/90 mm. Hg.

The electrocardiogram showed atrial fibrillation and digitalis effect. On radiologic examination, generalized cardiomegaly was present, the left atrium being disproportionately affected. Valvular calcification was not detected.

Cardiac catheterization with saline manometry revealed a cardiac output of 2.5 liters per minute. Thyrotoxicosis was excluded by the low cardiac output and negative tests for hyperthyroidism available at the time. A diagnosis of *silent rheumatic valvular disease* and systemic hypertension was made.

Thereafter the patient was admitted on five occasions because of congestive cardiac failure. On her second admission in 1953, the blood pressure was 160/70 mm. Hg and the heart had become grossly enlarged, with the apex in the seventh intercostal space in the mid-axillary line. A harsh systolic murmur was now audible over the whole of the front of the chest, but maximal at the apex. On her next admission in 1954, a mid-diastolic apical murmur was audible and the blood pressure was 195/105 mm. Hg. On her readmission in 1955, a systolic murmur was not heard but the diastolic murmur was audible. Her terminal admission in 1956, was associated with a blood pressure of 140/75 mm. Hg. A striking triple rhythm was present, with a Grade 3 systolic murmur at the apex.

At necropsy the heart weighed 482 grams and was markedly enlarged. The right atrium was dilated and was filled with postmortem clot. The coronary sinus admitted a thumb, and its orifice was traversed by Chiari's network. The atrial appendage was full of organizing thrombi, the tricuspid and pulmonary valves were healthy, and the right ventricle was not obviously hypertrophied. The left atrium was thin-walled but enormously dilated with focal nodularities and thickening suggesting old organized mural thrombi. The mitral valve admitted three fingers readily (Fig. 1). There was no stenosis. The mitral valves were thickened and distorted. The chordae were fused, thickened, and shortened with fibrosis of the papillary muscles; the left ventricular wall measured 1.6 cm. and was hypertrophied. Congestive cardiac failure was marked, with fine cirrhosis of the liver and pulmonary congestion. Microscopic examination showed hypertensive vascular changes in the kidneys and the adrenals. The changes in the papillary muscles, chordae, and mitral valves were conceded to be rheumatic in origin.

Case 2. A. D., a 33-year-old Malay male, was first seen in February, 1957. He had been quite well until 9 months previously, when he began to feel short of breath on effort. At first this was slight, but deterioration was progressive. In November, 1956, he had an attack of paroxysmal nocturnal dyspnea, and thereafter the attacks recurred almost nightly, so that he was forced to give up his work. There was no history of rheumatic fever. On examination at the Medical Outpatients' Department he was found to be in cardiac failure, with gross dyspnea, for which mercurials and digitalis were administered. No murmurs were audible at that time. The electrocardiogram showed left ventricular damage.

When he was examined in the Cardiac Clinic a month later, the jugular venous pressure was found to be considerably elevated, and hepatomegaly was still present. The pulse was normal, and the blood pressure was 140/100 mm. Hg. The apex beat was in the fifth intercostal space in the anterior axillary line, and was left ventricular in type. *No murmurs were audible.* Screening showed disproportionate left atrial enlargement, a large left ventricle, and hilar congestion. The cause of the heart failure was obscure, but a diagnosis of silent mitral incompetence was entertained.

The patient remained under regular treatment, and after 18 months was still edematous, with hepatomegaly and an apical triple rhythm but no murmurs. In May, 1960, he was admitted for cardiac catheterization; the signs and symptoms were completely unchanged. The phonocardiogram showed a loud third heart sound but no murmurs (Fig. 2,*A*). By now atrial fibrillation had developed, the left ventricle had enlarged further, and marked left atrial enlargement was still present on x-ray examination (Fig. 3,*A*).

At cardiac catheterization, the right atrial pressure was 11/5 mm. Hg, with a mean of 7, and a CV wave of 3 mm. The right pulmonary arterial wedge pressure was 42/22 mm. Hg, with a mean of 25, a CV wave of 20 mm., and a sharp Y descent (Fig. 4,*A*). The pulmonary arterial pressure was 55/25, the radial arterial pressure 135/75, and the left ventricular pressure 125/12 to 25 mm. Hg. Simultaneous diastolic pressures from the right pulmonary arterial wedge and left ventricle showed a 2-mm. diastolic gradient, which was probably due to the difference in manometric levels; the pressures were 22-27 and 20-25 mm. Hg, respectively (Fig. 5). There was no gradient between the left ventricle and aorta. The cardiac output was 3 liters per minute, and atrial fibrillation was present.

The injection of 50 c.c. of 90 per cent Hypaque into the left pulmonary artery barely outlined the pulmonary arteries and veins because of the very slow circulation. Cardiogreen injected into the left ventricle and aorta, with sampling from the femoral artery, showed curves of nearly normal contour. The left ventricular injection was slightly more spread out than the aortic, suggesting a large left ventricle or some mitral insufficiency. Both pulmonary arterial and superior vena caval injections produced very flat, spread out curves, with disproportionate prolongation of the disappearance slope, giving a CL:CR ratio of 0.85, which suggested a very large pulmonary and left atrial volume together with insufficiency of the mitral valve. The curve recorded after injection into the superior vena cava was not significantly different from that recorded after injection into the pulmonary artery, suggesting that the right heart volume was not unduly large and that there was no severe tricuspid or pulmonary incompetence.

The catheter findings thus indicated pulmonary venous hypertension secondary to an elevated left ventricular end-diastolic pressure, with no mitral valvular gradient during diastole. The wedge contour and dye curves suggested a significant degree of mitral insufficiency. The diagnosis made was silent mitral incompetence with atrial fibrillation, presumably due to rheumatic mitral valvular disease. Mitral incompetence secondary to cardiopathy of unknown origin could not be excluded.

Case 3. P. F., a 41-year-old white woman, was seen in September, 1957. When she was 18 years old, an anesthetist had first drawn her attention to a cardiac murmur. There had been no history of rheumatic fever prior or subsequent to this. She had a normal pregnancy, but about 13 years before admission she had noticed palpitations for the first time. In 1952, she developed paroxysmal disturbances of rhythm and was found to have atrial fibrillation but no evidence of heart failure. Three years later she was forced to give up playing tennis because of dyspnea. This was followed by increasing symptoms, which progressed to swelling of the feet and abdomen, necessitating digitalization, diuretics, and hospitalization.

On examination she was in gross heart failure, with marked venous congestion, tricuspid incompetence, and hepatomegaly. Atrial fibrillation, under digitalis control, was present. The apex was quiet, with right ventricular activity medially and a lift over the pulmonary outflow tract. On auscultation

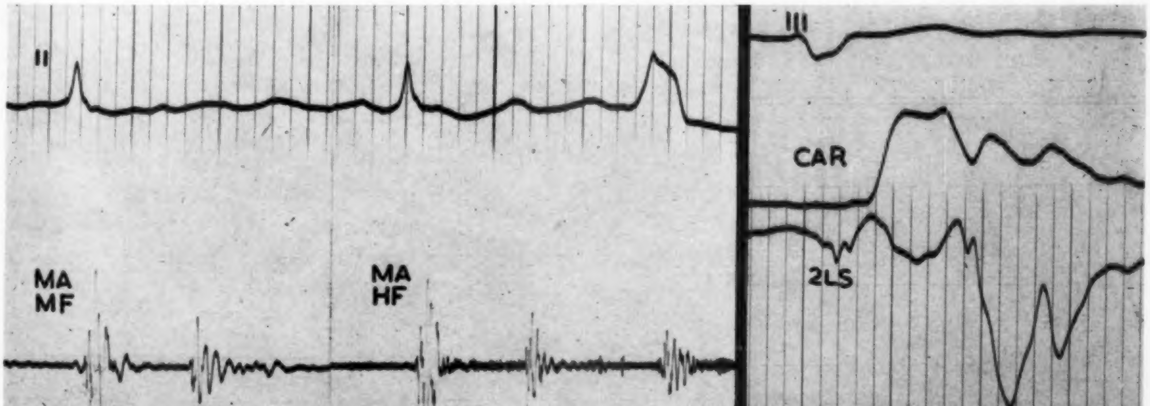

Fig. 2. Phonocardiograms at the mitral (*MA*) and fourth left intercostal space (*4LS*), high frequency (*HF*) and medium frequency (*MF*), from Case 2 (*A*) and Case 3 (*B*). Atrial fibrillation is present in both. In Case 2(*A*) a third heart sound is recorded but there are no murmurs. (Base-line artefact is present.) In Case 3 (*B*) a pansystolic murmur is present at the fourth left intercostal space, with wide splitting of the second sound, but no murmur is shown at the mitral area. The external carotid arterial tracing (*CAR*) and "apex cardiogram" from the second left intercostal space (*2LS*) are synchronously recorded.

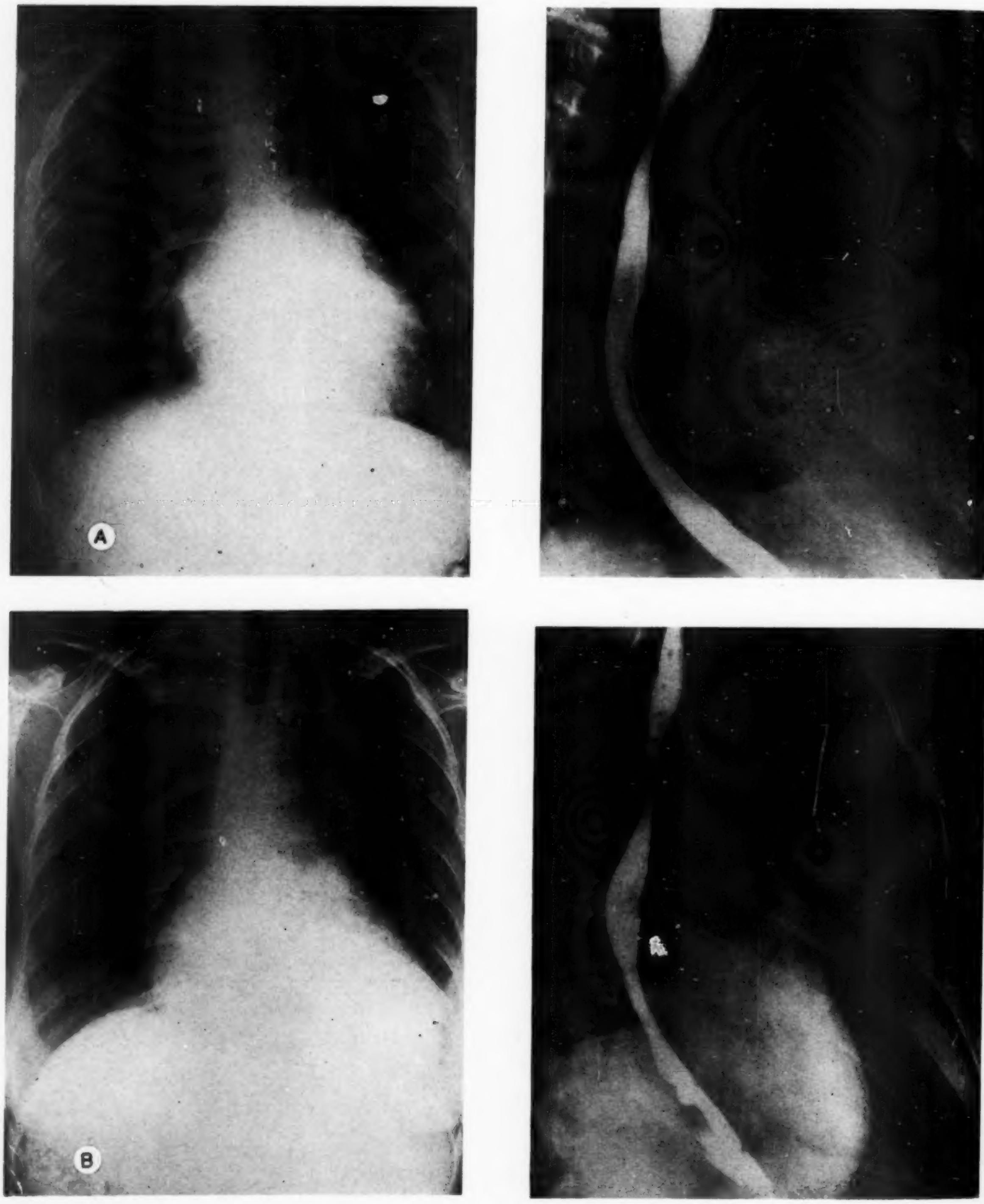

Fig. *3*. Anteroposterior and left oblique views from Case 2(*A*) and Case 3 (*B*). Disproportionate left atrial enlargement is present in both.

there was a widespread triple rhythm audible at all areas. After she exercised, the third sound became murmur-like, and a soft systolic murmur appeared. Phonocardiography (Fig. 2,*B*) showed a tricuspid systolic murmur, wide splitting of the second sound, but no mitral systolic murmur. The electrocardiogram showed combined heart strain with digitalis effect. On x-ray examination, moderate cardiomegaly was present, with disproportionate left atrial enlargement (Fig. 3,*B*).

At cardiac catheterization the mean right atrial pressure was 22 mm. Hg, with a CV wave of 13-22 mm., indicative of tricuspid incompetence. The right pulmonary arterial wedge tracing showed a

CV wave of 15 mm., with a sharp Y descent and a mean of 35 mm. Hg (Fig. 4,*B*). The pulmonary arterial pressure was 50/30, the right ventricular pressure 51/6-17, and the femoral arterial pressure 100-120/77 mm. Hg. Atrial fibrillation was present. The cardiac output was 3.4 liters per minute, and the tricuspid valve was normally situated. The catheter findings thus indicated pulmonary venous hypertension with significant mitral incompetence, and moderate pulmonary arterial hypertension with significant tricuspid incompetence. Ebstein's anomaly, which was one clinical suggestion, was excluded.

The diagnosis at the time of the patient's discharge was silent mitral incompetence, presumably due to rheumatic mitral valvular disease, with atrial fibrillation. Necropsy was not performed when she died some months later.

Case 4. N. S., a 53-year-old white male physician, was first seen in June, 1959, at the age of 53 years, with the following history. As a medical student 34 years before, he first became aware of premature systoles. He was seen by Sir Maurice Cassidy at that time and was told that he had no heart disease. Seven years later he developed asthma, from which he suffered for many years, finally developing several attacks of status asthmaticus associated with chronic emphysema. For the past 10 years, since he has been in Cape Town, he has been free of actual asthmatic attacks, although he has suffered from chronic wheezing and dyspnea. In 1948, he woke up one night with an attack of paroxysmal tachycardia, and on examination shortly afterward was found to have developed atrial fibrillation. In June, 1951, after an unsuccessful attempt at quinidine conversion, he was digitalized and has been kept on a maintenance dose ever since. The electrocardiogram showed atrial fibrillation, right axis deviation, ventricular ectopic beats, left ventricular hypertrophy, and digitalis effect. X-ray examination showed moderate cardiac enlargement, with a "mitral" contour, and disproportionate left atrial enlargement. *No murmurs were audible at any time.* In June, 1958, he was readmitted to the hospital for noncardiac reasons, and again there were no abnormal auscultatory findings. In September, 1959, he had an attack of pyrexia, followed by the signs and symptoms of congestive cardiac failure.

On examination he was in right heart failure. The jugular venous pressure was elevated to 20 cm., with the CV waves of tricuspid incompetence, and the liver was distended five fingerbreadths. Atrial fibrillation was present, with numerous ectopic beats, and the blood pressure was 115/70 mm. Hg. The apex was in the sixth intercostal space, 1 inch beyond the anterior axillary line, and was left ventricular thrusting in character. The first heart sound was normal in intensity, and, on occasion, a Grade 1-2[10] pansystolic murmur was audible at the mitral and tricuspid areas.

The electrocardiogram showed atrial fibrillation, ventricular ectopic beats, combined heart strain, and digitalis effect. The x-ray film (Fig. 6,*A*) showed very striking cardiomegaly, with almost aneurysmal dilatation of the left atrium; calcification of the mitral valves was not seen. Comparison with previous plates taken in 1951 showed a quite definite increase in the size of the heart.

Recent examination has shown improvement in symptoms but no change in the heart size. A very soft (Grade 1) short murmur was present at the mitral and tricuspid areas, and phonocardiography showed coupling due to ventricular premature systoles but no mitral systolic murmur (Fig. 7,*A*).

Case 5. C. W., a 35-year-old Coloured woman, was first seen on Aug. 30, 1957. She had been quite well until 2 weeks before, when she developed an influenza-like illness, with sore throat, body pains, pyrexia, and sweating. She stayed in bed for 2 days. On the third day she returned to work but did not feel well. On the fourth day she suddenly noticed swelling of the abdomen, and pain in the chest, which was worse when she coughed or breathed deeply. A day later her legs and face began to swell. From then on, progressive dyspnea developed and paroxysmal nocturnal dyspnea ensued. Herpes of the abdominal wall, anorexia, and vomiting were the other symptoms.

On admission to the hospital she was obese, orthopneic, and in congestive failure, with edema, raised venous pressure, and hepatomegaly. The

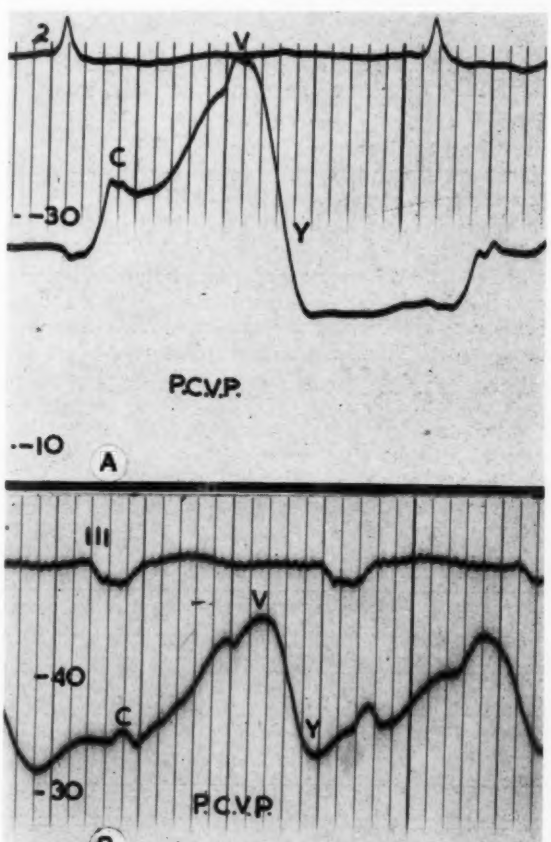

Fig. 4. Right pulmonary arterial wedge pressure recordings from Case 2(*A*) and Case 3 (*B*). The markedly elevated pressure is shown in both with a dominant CV wave of mitral incompetence and a sharp Y descent. Atrial fibrillation is present in both patients.

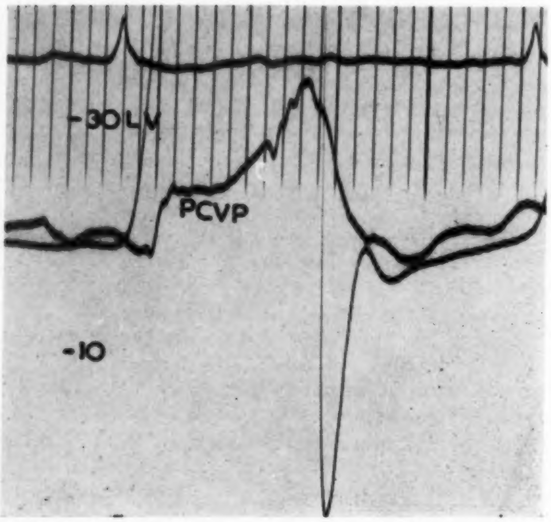

Fig. 5. Synchronously recorded right pulmonary arterial wedge and left ventricular pressures, showing the high end-diastolic pressure in the left ventricle, the absence of a diastolic gradient, and the presence of a large CV wave of mitral incompetence.

blood pressure was 140/80 mm. Hg. *No murmurs were audible,* but a triple rhythm was present. The electrocardiogram showed left atrial enlargement and left ventricular damage. X-ray examination showed cardiomegaly, with prominent pulmonary arteries.

When she was seen in the Cardiac Clinic a week later, the blood pressure was 130/90 mm. Hg, and she was no longer in cardiac failure. The first sound was palpable and accentuated, and the second sound was split, with accentuation of the pulmonary component (Fig. 7,*B*). Screening showed large pulmonary arteries and disproportionate left atrial enlargement.

She was examined on several occasions thereafter, and at no time were any murmurs noted. The electrocardiogram remained abnormal, with persistence of left atrial hypertrophy and left ventricular damage. A diagnosis of acute myocarditis was made, with acute heart failure and silent mitral incompetence.

After discharge she remained well without treatment, and apart from dyspnea on moderate effort she was symptom-free. Early in August, 1960, however, her symptoms returned, and she was admitted with ankle edema and abdominal swelling. The physical signs were the same as on her first admission, with edema, jugular venous distention, hepatomegaly, pleural effusion, and proteinuria. Cardiomegaly was again noted clinically and radiologically, with disproportionate left atrial enlargement (Fig. 6,*B*). The heart sounds were unchanged, and there were no murmurs.

The diagnosis made was silent mitral incompetence in association with myocardial failure of unknown origin.

Case 6. J. S., a 35-year-old unemployed Coloured man, was first seen in July, 1955. Three years before, he had developed hemoptysis, for which he had attended a tuberculosis clinic, and despite repeatedly negative sputa had been treated with streptomycin and, later, isoniazid. X-ray films were always negative for tuberculosis. About once a month he was subject to attacks of paroxysmal nocturnal dyspnea, which lasted half an hour at a time, but during the day his effort tolerance was reasonably satisfactory. Frequently repeated hemopytsis was a striking symptom.

On examination of the patient the jugular venous pressure was normal, and there was no evidence of heart failure. The pulse was normal and the blood pressure was 130/90 mm. Hg. The apex was left ventricular in type, in the normal site; a Grade 1-2 first heart sound was present, with a long Grade 2/4 diastolic murmur and a suspended presystolic murmur associated with first-degree block. *No murmur was audible in systole,* on careful auscultation. Nor was there an opening snap. The signs suggested fibrotic or calcified mitral valves, but calcium could not be seen on screening. The left atrium was enlarged radiologically and electrocardiographically. Operation was deferred.

The patient returned to work, but soon developed acute nocturnal dyspnea with pulmonary edema, for which he was admitted to a tuberculosis hospital, where he had several episodes of hemoptysis and was kept in bed for 5 weeks before transfer. On examination he was now found to have developed atrial fibrillation and a very soft Grade 1/6 apical systolic murmur. The other signs were virtually unchanged. An operation was advised after digitalization and diuretic therapy. At operation the pulmonary artery was found to be slightly larger than the aorta, with a pressure of 35/15 mm. Hg. The pressure in the left atrium was at least 25 mm. Hg, with large CV waves of mitral incompetence. Intracardiac palpation of the mitral valve revealed a systolic thrill and systolic jet, with calcification around the margin of the valves. The orifice of the valve was at least 3.5 cm. in diameter, and operation on the mitral valve was not attempted. The postoperative course was satisfactory; the arrhythmia was temporarily corrected with quinidine but soon reverted to atrial fibrillation. For the first 2 postoperative months he felt much improved. Reexamination of him as an outpatient showed a Grade 2/6 mitral systolic murmur and a Grade 2/4 mid-diastolic murmur at the apex. He failed to reattend until a year later, when he reported with a return of symptoms. For 3 months he had been having recurrent attacks of paroxysmal nocturnal dyspnea, and a week prior to admission he had experienced frequent palpitations. Examination revealed the rhythm disturbance to be that of flutter with varying block; there was virtually no systolic murmur audible at the apex. He was digitalized and discharged after 4 days. Five months later he returned with paroxysmal nocturnal dyspnea, hemoptysis, and progressive dyspnea. He now had atrial fibrillation, and, on auscultation, a Grade 1-2 systolic murmur was audible at the apex. Treatment was continued and he was not seen for a year, when he reported with a recurrence of symptoms. On this occasion a Grade 2-3 mitral systolic murmur had become clearly audible. A year later his condition was unchanged.

Discussion

Six cases of severe mitral incompetence with no murmur of mitral incompetence have been presented. In the first case, cardiac catheterization was performed to exclude thyrotoxicosis as a cause of obscure heart failure with atrial fibrillation and a nodular goiter. The disproportionate enlargement of the left atrium radiologically suggested rheumatic valvular disease, and this was proved at necropsy 5 years later when gross rheumatic valvular disease with pure mitral incompetence was demonstrated. The absence of murmurs could not be entirely attributed to the low cardiac output and severe heart failure, since the condition remained silent even when the patient had improved and was well enough for discharge. Moreover, as her condition deteriorated and her blood

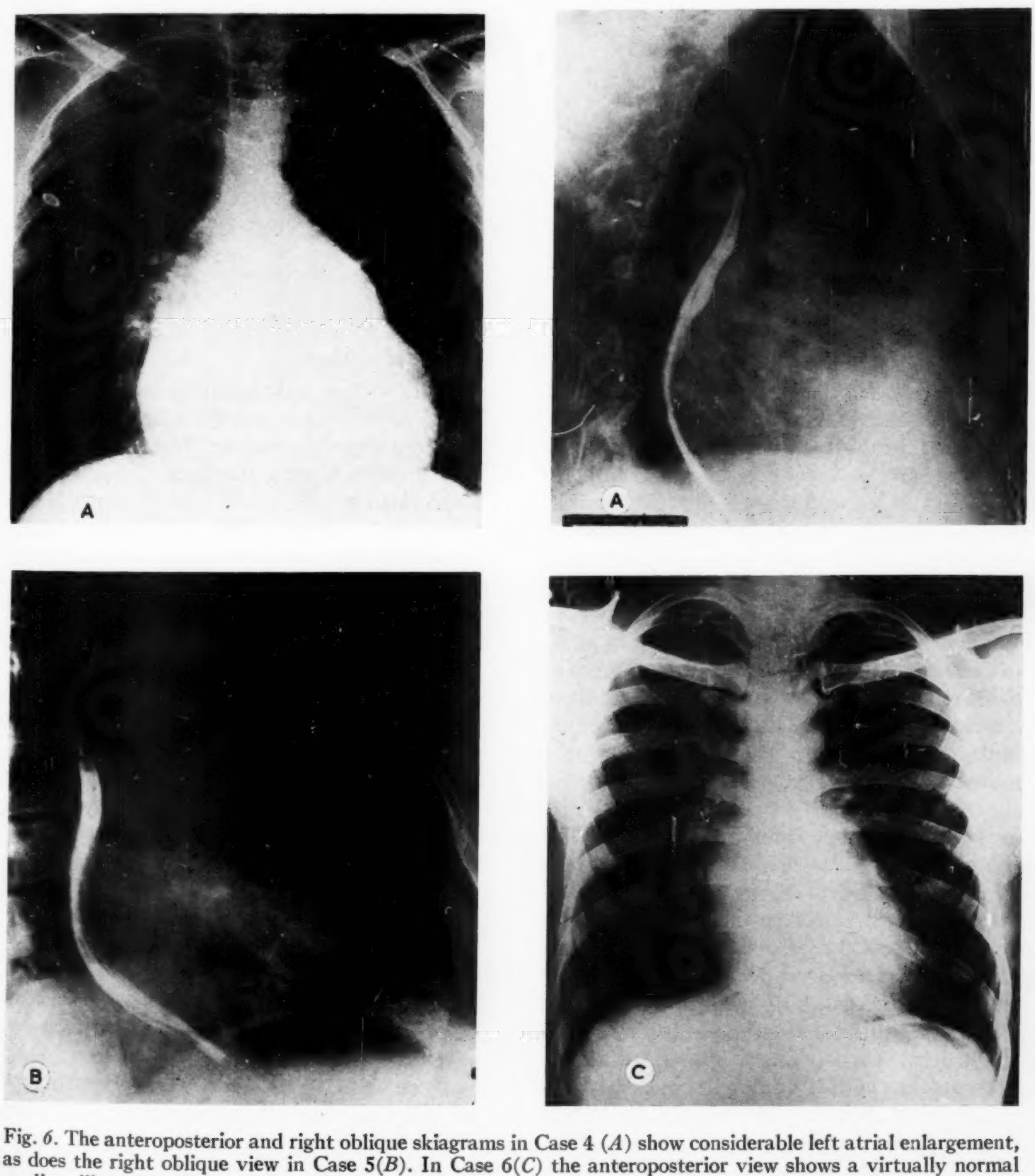

Fig. 6. The anteroposterior and right oblique skiagrams in Case 4 (*A*) show considerable left atrial enlargement, as does the right oblique view in Case 5(*B*). In Case 6(*C*) the anteroposterior view shows a virtually normal cardiac silhouette.

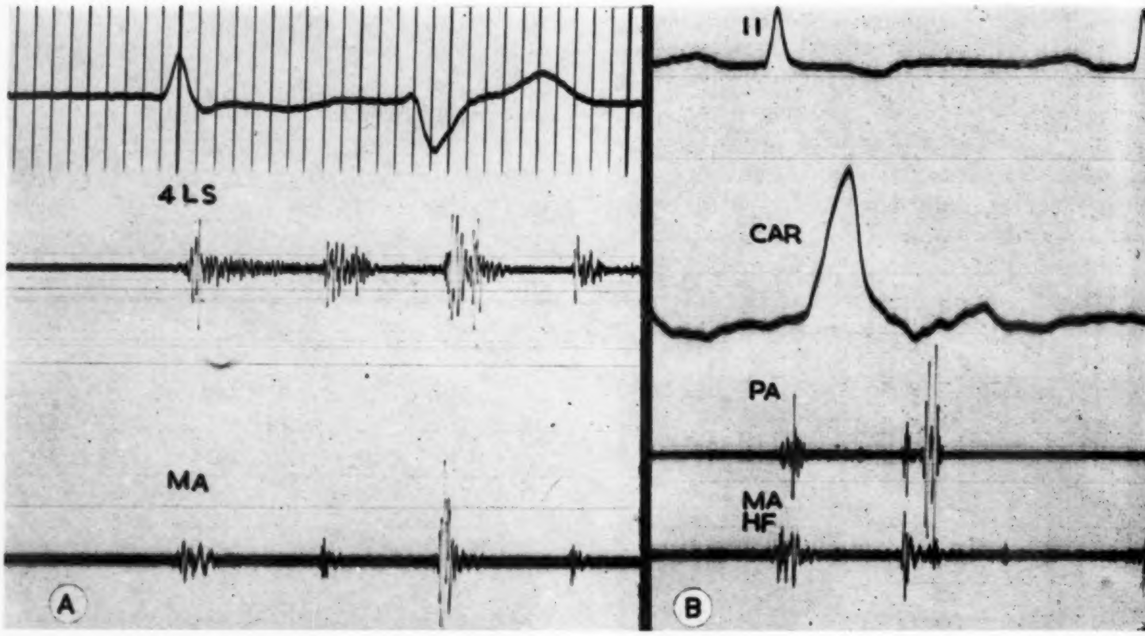

Fig. 7. Phonocardiograms from Case 4 (*A*) and Case 5 (*B*) show no murmur at the mitral area (*MA*). In *A* there is a pansystolic murmur at the tricuspid area (*4LS*). Atrial fibrillation with coupling due to ventricular ectopic beats is present. Wide splitting of the second heart sound is shown in both cases.

pressure fell from hypertensive to normotensive levels, thus diminishing the gradient between the left ventricle and the left atrium, mitral murmurs became audible both in systole and diastole.

The second patient was examined repeatedly both during sinus rhythm and atrial fibrillation over a period of 3½ years. Cardiac failure was always present and cardiac output was less than normal; nevertheless, his condition was never so bad as to reduce mitral valvular flow to an absolute minimum. The absence of murmurs could hardly be attributed to the severity of the heart failure per se. As in the first case, disproportionate enlargement of the left atrium radiologically was the clue to the diagnosis, and during sinus rhythm, left atrial hypertrophy was confirmed electrocardiographically. The diagnosis was proved by cardiac catheterization, with the demonstration of severe left atrial hypertension with a dominant CV wave of 20 mm. Hg and no diastolic gradient across the mitral valve. The high end-diastolic pressure in the left ventricle confirmed the presence of left ventricular failure. Dye-dilution curves strongly supported the diagnosis of mitral valvular insufficiency. Although the exact etiology is obscure and rheumatic heart disease cannot be proved short of necropsy study, the presence of a severe degree of mitral insufficiency was firmly established.

A murmur was heard during youth in the third patient, but 20 years thereafter, when she began to develop symptoms, it was inaudible. A few years later, during the period of study when she was in heart failure with atrial fibrillation, there were no apical murmurs. The presence of a soft systolic murmur at the tricuspid area, with heart failure of obscure origin and diminished pulmonary blood flow, raised the question of Ebstein's anomaly, and one of the reasons for cardiac catheterization was to exclude this diagnosis. The electrocardiographic findings and the presence of left atrial enlargement radiologically, although not quite so great as in the other cases, suggested the presence of mitral incompetence. At cardiac catheterization the diagnosis of severe mitral and tricuspid incompetence was established, with moderate hypertension and a reduced cardiac output. The pulmonary wedge pressure revealed severe pulmonary venous hypertension with a dominant CV wave of 15 mm. Since the gradient across the mitral valves was not measured, the pres-

ence of additional mitral stenosis could not be excluded.

The fourth patient was known to have had an irregular heart action for 34 years but was unaware of heart disease. When atrial fibrillation developed and became established, no murmurs were heard. Only after repeated admissions and examinations was an inconstant soft systolic murmur observed over the anterior aspect of the chest. Phonocardiography showed a systolic murmur at the tricuspid area but none at the mitral area. The presence of disproportionate and progressive enlargement of the left atrium was again the clue to the diagnosis.

In the fifth patient the diagnosis was made entirely on radiologic grounds. Repeated examinations during two separate episodes of heart failure over a period of 3 years failed to reveal any murmurs. Disproportionate left atrial enlargement was always present on x-ray examination, and the electrocardiogram confirmed the presence of left atrial hypertrophy. The etiological diagnosis remained obscure.

The sixth patient was referred for closed mitral valvotomy, with severe symptoms of heart failure attributed to obstruction at the mitral valve. A left ventricular apex beat suggested the presence of some degree of mitral incompetence, but there was no murmur in systole. In a series of over 300 patients examined by one of us (V.S.) and submitted to mitral valvotomy this has been the only patient with significant mitral incompetence and no systolic murmur. At operation, severe mitral incompetence was considered to be the sole lesion. The absence of a systolic murmur could not be attributed to poor myocardial function and a low cardiac output, since a murmur was inaudible during his first examination when he had minimal symptoms and sinus rhythm.

Since mitral incompetence was silent, all but the sixth patient presented the problem of heart failure of unknown origin. Were it not for the disproportionate left atrial enlargement, mitral incompetence would have been missed. Only in the last case did a mitral diastolic murmur draw attention to valvular heart disease; here the unusual feature was the lack of a systolic murmur despite gross mitral incompetence found at the time of operation. It is believed that cases of "heart failure of unknown origin" which show disproportionate left atrial enlargement should be investigated for mitral incompetence, even in the absence of murmurs. If incompetence is gross, mitral annuloplasty may be feasible.

Wood[11] has reviewed his experience in a careful and detailed study of 300 patients with mitral valvular disease. There was no patient with significant mitral insufficiency in whom a systolic murmur was not heard, and he concluded that, "It can no longer be seriously maintained that a mitral systolic murmur is of little value in determining the presence or absence of mitral incompetence." A loud pansystolic murmur was found in all 30 cases of mitral incompetence described by Brigden and Leatham,[1] and in the 23 cases of Ross and associates,[12] but these cases were probably selected on the basis of a murmur. Venner and Holling[13] never encountered at operation a wide rigid orifice without a systolic murmur. Recent reviews on mitral incompetence[14,15] have again stressed the importance of the mitral systolic murmur, and intracardiac phonocardiographic study[16] has confirmed the presence of this murmur in the left atrium near the orifice of the mitral valve. It is generally agreed, however, that the severity of the incompetence cannot be assessed from the intensity of the murmur,[17] although, generally speaking, the loudest murmurs are associated with the severest degree of regurgitation. The louder the murmur the more likely it is to be due to mitral incompetence.[18] Incompetence, on the other hand, may be severe in the presence of slight murmurs.

In contrast, Logan and Turner[19] claim that the absence of a mitral systolic murmur does not exclude significant mitral incompetence. Thus, of 17 cases in which a strong regurgitant jet was felt at operation, "no murmur had been recorded" in one.[20] Similar statements have been made by others.[21,22] Most of this evidence comes from cases of mixed mitral valvular disease (such as our Case 6) referred for closed mitral valvotomy.

That mitral incompetence can occur in the absence of a systolic murmur has been amply demonstrated in this series of cases.

The degree of incompetence was gross in every case, and it may well be that severe mitral incompetence, like tricuspid incompetence,[23,24] can occasionally be silent. The degree of incompetence is probably a more important factor than the presence of cardiac failure, atrial fibrillation, or any myocardial (muscular) factor.

Summary

1. A systolic murmur, usually described as loud and holosystolic, is the conventional hallmark of mitral incompetence.

2. Six cases of silent mitral incompetence are described, in which murmurs were absent at the apex despite the presence of gross mitral regurgitation. In three cases, despite frequent examination over long periods, no murmurs could be heard or recorded by phonocardiography at any time. In the other three, soft mitral systolic murmurs were sometimes present and sometimes absent.

3. Heart failure and atrial fibrillation did not appear to be responsible for these findings.

4. In all six patients, radiologic examination showed disproportionate enlargement of the left atrium and provided the clue to the correct diagnosis.

5. Rheumatic mitral valvular disease was proved at necropsy in one and at operation in another. Cardiac catheterization established the diagnosis but not the etiology in two.

6. Gross mitral incompetence can occur in the absence of any audible systolic murmur.

We wish to thank members of the Staff of Groote Schuur Hospital for referring cases for investigation, and the Superintendent, Dr. J. Burger, for permission to publish. We acknowledge the great help received from our Chief Technician, Mr. L. W. Piller, and his associates, Mr. R. deMeneau and Miss S. Joseph in the cases catheterized.

REFERENCES

1. Brigden, W., and Leatham, A.: Mitral incompetence, Brit. Heart J. **15**:55, 1953.
2. Steell, G.: Textbook on diseases of the heart, Manchester, England, 1906, Manchester University Press.
3. MacKenzie, J.: Principles of diagnosis and treatment of heart affections, London, 1916, Oxford Medical Publications.
4. Lewis, T.: Diseases of the heart, London, 1933, The Macmillan Company.
5. Evans, W.: Cardiology, London, 1948, Butterworth, Ltd.
6. Sprague, H. B., and White, P. D.: A comparative study of "rheumatic" mitral regurgitation and mitral stenosis, AM. HEART J. **1**:629, 1926.
7. Boone, J. A., and Levine, S. A.: The prognosis in "potential rheumatic heart disease" and "rheumatic mitral insufficiency," Am. J. M. Sc. **195**:764, 1938.
8. Fishberg, A. M.: Heart failure, ed. 2, Philadelphia, Lea & Febiger.
9. Master, A. M.: Apical systolic murmur, Arch. Int. Med. **81**:518, 1948.
10. Freeman, A. R., and Levine, S. A.: The clinical significance of the systolic murmur, Ann. Int. Med. **6**:1371, 1933.
11. Wood, P.: An appreciation of mitral stenosis, Parts 1 and 2, Brit. M. J. **1**:1051 and 1113, 1954.
12. Ross, J., Braunwald, E., and Morrow, A. G.: Clinical and haemodynamic observations in pure mitral insufficiency, Am. J. Cardiol. **2**:11, 1958.
13. Venner, A., and Holling, H. E.: Comparison of operation and clinical findings in mitral stenosis and incompetence, Brit. Heart J. **15**:205, 1953.
14. Van der Veer, J. B.: Mitral insufficiency. Historical and clinical aspects, Am. J. Cardiol. **2**:5, 1958.
15. Bleifer, S., Dack, S., and Grishman, A.: The auscultatory and phonocardiographic findings in mitral regurgitation, Am. J. Cardiol. **5**:836, 1960.
16. Lui, C. K., Aravanis, C., Testelli, M. R., and Luisada, A. A.: Intracardiac phonocardiography in mitral and aortic valve lesions, Am. J. Cardiol. **1**:379, 1958.
17. Ellis, L. B., Abelmann, W. H., and Harken, D. E.: Selection of patients for mitral and aortic valvuloplasty, Circulation **15**:924, 1957.
18. Burchell, H. B., and Edwards, J. E.: Rheumatic mitral insufficiency, Circulation **7**:747, 1953.
19. Logan, A., and Turner, R.: The diagnosis of mitral incompetence accompanying mitral stenosis. Review of eleven cases treated surgically, Lancet **2**:593, 1952.
20. Logan, A., and Turner, R.: Mitral stenosis. Diagnosis and treatment, Lancet **1**:1006 and 1057, 1953.
21. Dexter, L., McDonald, L., Rabinowitz, M., Saxton, G. A., and Haynes, F. W.: Medical aspects of patients undergoing surgery for mitral stenosis, Circulation **9**:758, 1954.
22. Schilder, D. P., and Proctor, Harvey, W.: Confusion of tricuspid incompetence with mitral insufficiency—a pitfall in the selection of patients for mitral surgery, AM. HEART J. **54**:352, 1957.
23. Aceves, S., and Carral, R.: The diagnosis of tricuspid valve disease, AM. Heart J. **34**:114, 1947.
24. Muller, O., and Shillingford, J.: Tricuspid incompetence, Brit. Heart J. **16**:194, 1954.

The genesis of bidirectional tachycardias

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Several mechanisms for the production of bidirectional tachycardias have been proposed.[1-11] This is not surprising in view of the uncertain origin of arrhythmias which have a rapid rate with prolonged and bizarre QRS complexes.[12] As in all cases of complex disorders of rhythm a complete knowledge of cardiac physiology is required. But, in addition, the technician should be taught to obtain long strips of the electrocardiogram, mainly in one lead, so that the greatest number of pathologic mechanisms can be recorded, as can be seen in Figs. 1-7 of this communication.

Because of the complexities seen in short (conventional) tracings, certain authors have advanced the theory that bidirectional tachycardia probably represents a heterogeneous group of cases which have similar electrocardiographic configuration.[1] For example, some workers have postulated the existence of two pacemakers: either one supraventricular and one ventricular[2,3] or two ventricular ones.[7,8,21] Moreover, others believe that the paroxysm originates in one single focus before[1,4,5,6,9-11,13] or after the bifurcation.[14,22] Precisely, this communication establishes that not one,

Table I

Case	*Age (yr.)*	*Etiology*	*Heart failure*	*Digitalis*	*Atrial rhythm during paroxysm*	*Esophageal leads*	*Alternation in direction in Lead* V_1	*Ventricular rate*
1.	63	AHD	Yes	++++	A. F.	Yes	No	157
2.	68	AHD	Yes	++++	A. F.	Yes	No	158
3.	70	AHD	Yes	++++	A. F.	Yes	No	150
4.	65	AHD	Yes	++++	S. R.	Yes	No	167
5.	88	AHD	Yes	++++	S. R.	Yes	No	150–172
6.	71	AHD	Yes	++++	A. T.	Yes	No	115
7.	75	AHD	Yes	++++	A. T.	Yes	No	168
8.	69	AHD	Yes	++++	A. T.	Yes	No	176–188
9.	71	EM	No	+	A-V. T.	No	No	167–180
10.	63	AHD	Yes	++	A-V. T.	Yes	No	170
11.	65	AHD	Yes	++++	A. F.	No	Yes	166
12.	84	AHD	Yes	++++	A. F.	Yes	No	166
13.	9	DM	No	No	?	No	No	130
14.	9	NH	No	No	A. T.	Yes	No	188–275

AHD: Arteriosclerotic heart disease. EM: Encephalomyocarditis. DM: Diphtheritic myocarditis. NH: Normal heart. A.F.: Atrial fibrillation. S.R.: Sinus rhythm. A.T.: Atrial tachycardia. A-V.T.: Atrioventricular nodal tachycardia.

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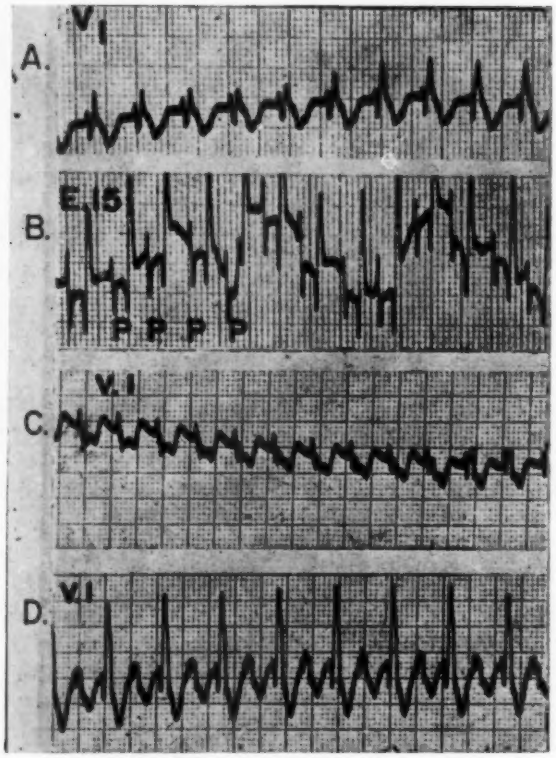

Fig. *1*. Bidirectional tachycardia of atrial origin. These tracings were obtained from a 9-year-old asthmatic girl with bouts of "repetitive paroxysmal tachycardia," but no heart disease. A supraventricular tachycardia (rate: 188 per min.) with aberration showing different degrees of right-sided intraventricular conduction defect can be seen in *A*. The esophageal lead (*B*) clearly establishes the atrial origin of the paroxysm. In *C*, different degrees of aberration are seen again. Finally, in *D*, when the rate speeded up to 275 per min., a curious form of alternation is present: an rsR′ complex of lesser duration and smaller height alternates with one of greater duration and height. This record is interpreted as an example of atrial tachycardia with bidirectional complexes due to alternating aberrant ventricular conduction. The warming up of the ectopic center is attributed to a mechanism similar to the "rhythm of development."[20]

but several mechanisms are involved in the genesis of what has been called bidirectional tachycardia from a simple morphologic configuration. Prognosis and treatment will not be considered here.

Material and methods

Our material consists of 14 records showing bidirectional tachycardias (other tracings from these patients have been included in previous reports[13,14]). All subjects except 3 (Table I) had arteriosclerotic heart disease and varying degrees of congestive failure. The detailed clinical data are presented in Table I. It is to be noted that esophageal leads were obtained simultaneously with a conventional lead, whenever the coexisting supraventricular rhythm *during* the paroxysm could not be ascertained with accuracy. The term "bidirectional tachycardia" as used in this report assumes the existence of a rapid ectopic rhythm with a rate ranging in 80 per cent of the cases from *150* to *188* (Table I) and rhythmical alternation of QRS complexes (either prolonged or normal), although such ventricular complexes are not necessarily inscribed in opposite direction in each lead. Generally, the rhythm is regular, but occasionally the rate, as well as the interval between the complexes of different morphologies, may vary more than 0.04 second.

Results

Of the 14 cases studied there were 5 in which the corresponding records showed certain characteristics which could be of help in clarifying the genesis of bidirectional tachycardias. These cases are presented in Figs. 1-7, and the corresponding electrocardiograms are fully described in the respective legends. Table I shows the basic features.

Comment

Many theories have been proposed to explain the genesis of bidirectional tachycardias.[1-14] Some have received widespread attention[1,2,6,9,11,12]; others, such as the double circus movement of White and Palmer,[15] have been practically forgotten. One of the earliest assumptions favored the ventricular origin of the paroxysm.[7,8] This was due to the observation that many cases showed frequent ventricular extrasystoles prior to or after the tachycardia. Thus, it was considered that the two morphologies corresponded to two foci of impulse formation, that is, one in each ventricle.

Such a theory has been challenged in later years since the work of Zimdahl and Kramer,[2] who showed that one of the two complexes in their case could be abolished by carotid sinus pressure, and thus postulated that two active centers were present—one ventricular and one supraventricular. Similarly, other authors

have since reported instances of disappearance of the arrhythmia by this or allied vagomimetic procedures.[2-5,13,16] However, the unquestionable ventricular origin of bidirectional tachycardia was established in Figs. 4 and 5 by the presence of fusion beats; the alternating complexes were explained on the basis of irregular intraventricular propagation. Furthermore, this case is a clear example of the abolishment of a ventricular tachycardia by carotid sinus pressure, so that the effectiveness of this procedure cannot be related necessarily to the existence of a supraventricular tachycardia.[1] It should be emphasized that Scherf[17,18] has reported the slowing of ventricular parasystole by carotid pressure, indicating the response of ventricular rhythms to vagus stimulation. Similarly, the transition of bidirectional to unidirectional complexes without changes in rate also rules out the diagnosis of double ventricular paroxysmal tachycardia. Evidently, this possibility is to be considered extremely rare because no instance of this arrhythmia was found in a recent review of 15 cases of simultaneous tachycardias.[14]

Occasionally, it has been considered that the disappearance of one type of beat, with halving of the ventricular rate after

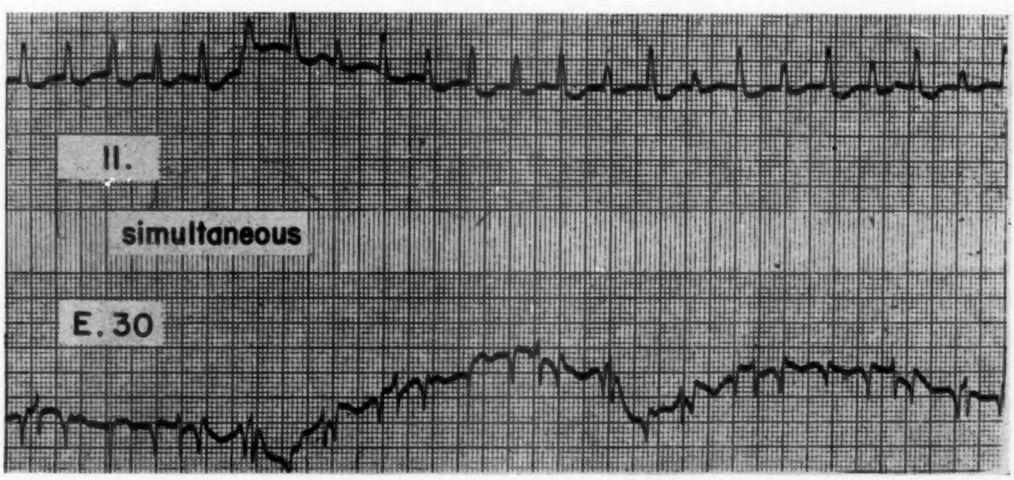

Fig. *2*. Bidirectional tachycardia originating in one supraventricular center, probably in the A-V node. The tracings start with a regular tachycardia (rate: 167 per min.) and QRS duration of 0.06 sec. Note that it is dissociated from an independent sinus rhythm (rate: 103 per min.), and that the P waves have a predominant negative deflection in the esophageal lead (*E. 30*). Alternation in the height of ventricular complexes appears toward the middle of the tracing and is best seen in Lead II. The records continue uninterruptedly with that of Fig. 3.

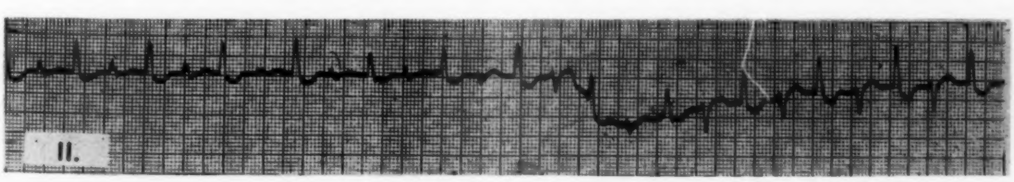

Fig. *3*. Bidirectional tachycardia originating in one supraventricular center, probably in the A-V node. This tracing is continuous with that of Fig. 2, and shows besides an alternation in the height of ventricular complexes a progressive alternation in direction of QRS and T, until the classic-image bidirectional tachycardia appears toward the end of the record. In Figs. 2 and 3 the strictly regular and constant rate, and the gradual evolution from unidirectional to bidirectional alternation, in association with only moderate changes in ventricular duration (which is within normal limits: 0.08 sec.) and rate, lend support to the assumption of a single supraventricular center with varying deviation of intraventricular propagation of rapid impulses in alternate cycles. The presence of an independent sinus rhythm is against the existence of a rapid atrial arrhythmia, and favors the diagnosis of A-V nodal tachycardia with varying intraventricular conduction. Similar QRS complexes of lesser duration (0.06 sec.) were seen in this patient after the return of normal basic rhythm.

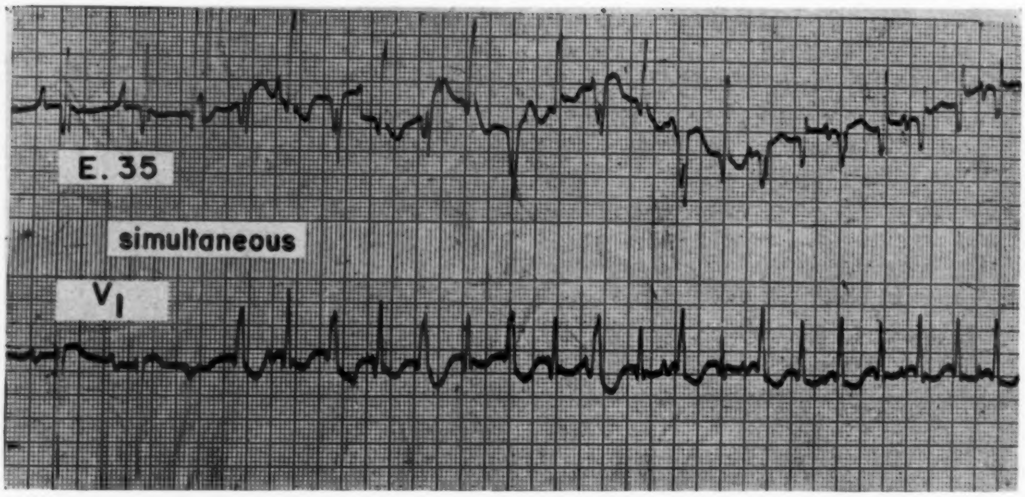

Fig. 4. Bidirectional tachycardia originating in one ventricular center. This tracing starts with two normally conducted sinus beats (rate: 91 per min.) which precede a run of bidirectional ventricular tachycardia (rate: 150 per min.). The most prominent finding in this record is the presence of alternation in direction of QRS complexes (its duration being 0.11 sec.) in the esophageal lead, whereas the simultaneously obtained Lead V_1 shows alternation in morphology and height only. Sinus activity persists at its usual speed, yet dissociated evidently from the ventricular complexes. A curious phenomenon is seen toward the end of the tracing: as the ventricular rate increases to 172 per min., alternation disappears completely (last three complexes), but with a decrease in QRS duration to 0.09 sec. On the basis of such findings it can well be assumed that the paroxysm arose in one center, occasionally with, and sometimes without, ventricular alternation. However, from an inspection of this tracing, the exact origin of the tachycardia (whether A-V nodal or ventricular) could not be ascertained.

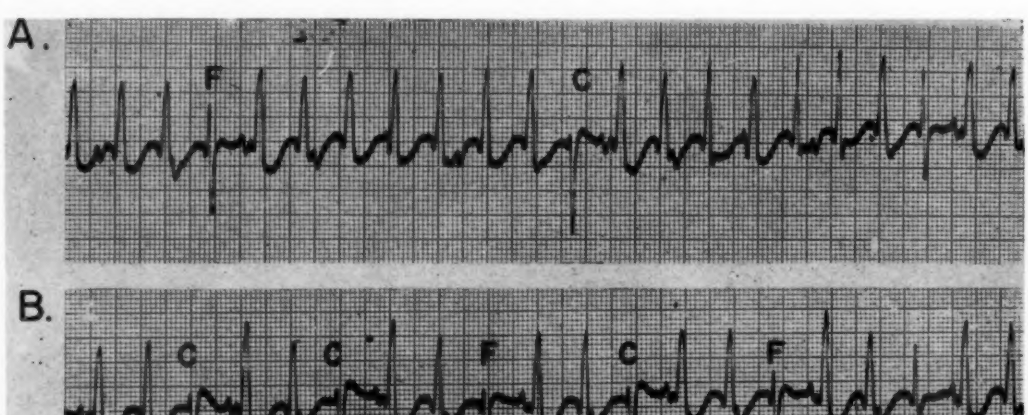

Fig. *5.* ECG from same patient as in Fig. 4. (*For legend see opposite page.*)

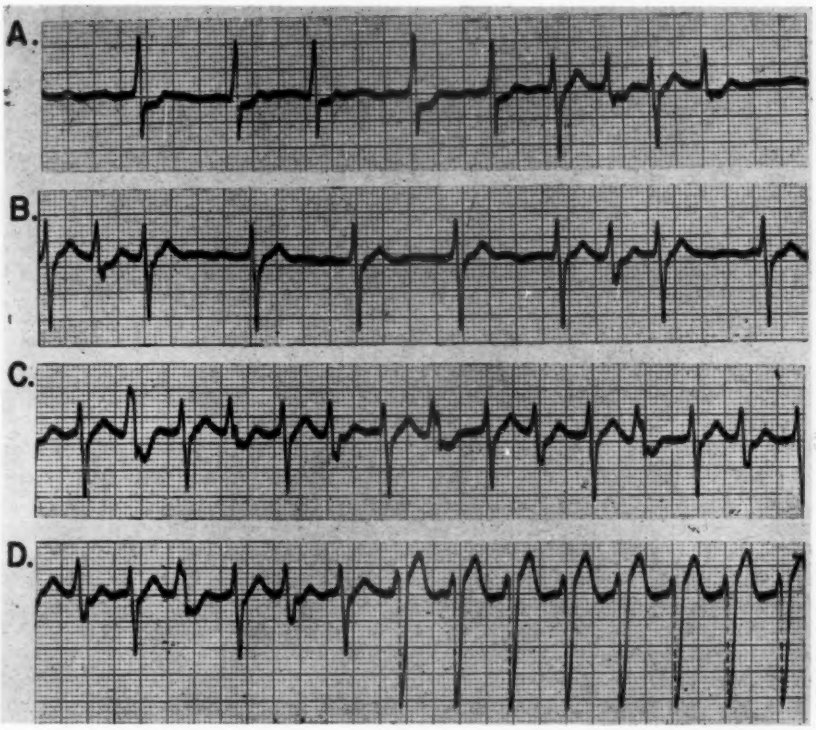

Fig. *6*. Bidirectional tachycardia originating in one center, probably ventricular (Lead II). *A* shows atrial fibrillation and normal ventricular rate interrupted by a short run of bidirectional tachycardia (last four beats), its rate ranging between 150 and 156 per sec. *B* starts with the same tachycardia, but now after the first three complexes it can be appreciated how, paradoxically, the smaller complexes vanish and the larger QRS complexes persist at a rate of 75 per min., which is exactly half of the tachycardia previously present. This phenomenon can well be explained by the presence of an intermittent 2:1 exit block from the ectopic center and is corroborated by the finding of another complex occurring midway between the seventh and eighth QRS complexes. The classic picture of bidirectional tachycardia can be observed throughout *C* and the beginning of *D*. Toward the middle of the latter tracing another puzzling alteration is observed: the alternating beats abruptly change in shape, so that other beats of a third morphology appear, the rate being exactly the same as that of the bidirectional tachycardia (150 per min.). This unusual arrhythmia as a whole can be interpreted as a ventricular tachycardia arising in one center, probably ventricular. The various morphologies of the QRS complexes are due to varying and irregular intraventricular propagation. A similar arrhythmia was previously reported.[14]

Fig. *5*. Electrocardiograms obtained from the same patient as was Fig. 4, and demonstrating the ventricular origin of the tachycardia (Lead V_1). *A* and *B*, recorded a few minutes after the preceding Fig. 4, show the same tachycardia, but now it is interrupted by ventricular captures (*C*) and fusion beats (*F*), which show that the ventricles are activated partly by the oncoming atrial stimulus and partly by the stimulus originating in the ectopic center. Such phenomenon convincingly proves the ventricular origin of the paroxysm. Finally, *C* records the end of the tachycardia after carotid pressure was applied. Posterior to such a vagal stimulation a fusion beat appears, followed by two idioventricular beats resembling those seen previously. This strip emphasizes that ventricular tachycardia can be stopped by carotid sinus pressure. Thus, the disappearance of an ectopic rapid rhythm by carotid sinus pressure does not necessarily indicate the ventricular origin of the arrhythmia as has been previously assumed. A similar effect on the rate of ventricular parasystole was reported by Scherf.[10,17]

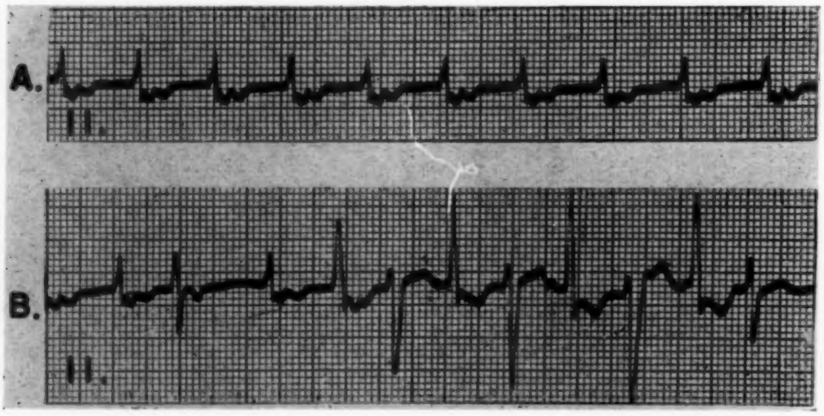

Fig. 7. Bidirectional tachycardia arising below the A-V node. *A* shows an A-V nodal tachycardia (rate: 125 per min.) and posterior stimulation of the atria, which was considered to originate in the lower regions of the A-V node. *B* starts with two A-V beats, followed by an extrasystole arising very late in the R-R cycle. It is followed by another nodal beat, which, in turn, precedes a run of bidirectional tachycardia. The ectopic paroxysm discharges the A-V center so that a simultaneous tachycardia does not exist. Since the pre-existing rhythm had its origin in the lower portions of the node, the second (ectopic) center must be located below this region. No conclusion can be definitely drawn as to whether we were dealing with one or two centers, either before or after the bifurcation of the common bundle.

vagal stimulation, proves the double origin of the paroxysm.[12] Yet, Fig. 6, as well as Fig. 13 of the article by Castellanos and associates,[14] show that 2:1 exit block from a single ectopic center accounts for such a phenomenon. Evidence of a unifocal center is present in Figs. 1 through 6.

Undoubtedly, bidirectional tachycardias can be of supraventricular origin, a theory postulated originally by Scherf and Kisch,[9] and convincingly proved by these authors in cases of atrial tachycardias,[9,10] and by Pick and Langendorf in instances of A-V nodal tachycardias.[11]

Fig. 1 is an example of atrial tachycardia with aberrant ventricular conduction. In some instances this functional intraventricular, right-sided, block shows persistent alternation, so that the typical image of bidirectional tachycardia is seen in Lead V_1.

In Figs 2 and 3 the slow change from unidirectional to bidirectional alternation, associated with only slight changes in QRS complexes of normal duration (0.08 second), supports the assumption of a supraventricular arrhythmia, showing intermittent intraventricular aberration.[11] Obviously, it could not arise in the atria, for these anatomic structures are activated by the sinus node, as seen in the esophageal lead.

Such findings, coupled with the fact that after the disappearance of the tachycardia the morphology of the QRS complex was similar to those in Fig. 2, lend support to the hypothesis which interprets the paroxysm as A-V nodal in origin. One main characteristic of bidirectional tachycardias was the finding of alternation in morphology, but not in direction, in Lead V_1 (Table I). The opposite finding was usually, but not always, seen in Lead II and at several esophageal levels. Nevertheless, Case 11 (Table I), and Fig. 9 of Pick and Langendorf's paper,[11] show alternation in both parameters in Leads V_1 and V_{3R}. Yet, positive complexes in Lead V_1, when present, would disprove the idea of a septal center equidistant to the two bundle branches, with alternating impairment of impulse propagation to the two bundle branches.[12] On the other hand, alternating complexes in right precordial leads are explained on the basis of functional right bundle branch block in instances of supraventricular tachycardias[12,19] (either atrial or A-V nodal) and on the basis of alternating irregular intraventricular propagation, if the arrhythmia is ventricular.[14]

Paroxysmal tachycardia of the bidirectional type as considered in this report

is usually, but not invariably, produced by digitalis intoxication. Table I presents evidence of 3 cases in which the main etiological factor was considered to be, respectively, encephalomyocarditis (Case 9), diphtheritic myocarditis (Case 13), and repetitive paroxysmal tachycardia with a normal heart (Case 14).

It should be emphasized that excessive digitalization was not the cause in 2 patients. In one the tachycardia appeared after small and proportional amounts of strophanthidin, acetylstrophanthidin, ouabain, and digoxin (Case 9), previously reported in Figs. 8, 9, and 10 of the paper of Castellanos and associates.[14]

Summary

Bidirectional tachycardia is a descriptive term indicating a tachycardia with alternation in morphology and (or) direction of QRS complexes. A review of 5 cases was made, from which it could be concluded that the paroxysm originates in a single pacemaker, either in the atria, in the A-V node, or in the ventricles.

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REFERENCES

1. Weinstein, W. J., and Jick, S.: Bidirectional tachycardia, Am. J. Cardiol. **3**:343, 1959.
2. Zimdahl, W. T., and Kramer, L. I.: On the mechanism of paroxysmal tachycardia with rhythmic alternation in the direction of ventricular complexes, Am. Heart J. **33**:218, 1947.
3. Zimdahl, W. T., and Townsend, C. T.: Bidirectional ventricular tachycardia due to digitalis poisoning, Am. Heart J. **47**:304, 1954.
4. Hellman, E., and Lind, A.: Bidirectional tachycardia, Am. Heart J. **51**:140, 1956.
5. Velazquez, J., and Kilser, G. A.: Alternating bidirectional tachycardia, Am. Heart J. **54**:440, 1957.
6. Luten, D.: Clinical studies of digitalis. III. Advanced toxic rhythms, Arch. Int. Med. **35**:87, 1925.
7. Felberbaum, D.: Paroxysmal ventricular tachycardia. Report of a case of unusual type, Am. J. M. Sc. **166**:211, 1923.
8. Schwensen, C.: Ventricular tachycardia as the result of the administration of digitalis, Heart **9**:199, 1922.
9. Scherf, D., and Kisch, B.: Ventricular tachycardias with variform ventricular complexes, Bull. New York. M. Coll. **2**:73, 1939.
10. Scherf, D., and Schott, A.: Extrasystoles and allied arrhythmias, New York, 1953, Grune & Stratton, Inc.
11. Pick, A., and Langendorf, R.: Differentiation of supraventricular and ventricular tachycardias, Prog. Cardiovas. Dis. **2**:391, 1960.
12. Katz, L. N., and Pick, A.: Clinical electrocardiography. Part I. The arrhythmias, Philadelphia, 1953, Lea & Febiger, Fig. 215.
13. Calviño, J. M., Azan, L., and Castellanos, A., Jr.: Valor de las derivaciones esofagicas en las arritmias complejas, Rev. cubana cardiol. **16**:293, 1955.
14. Castellanos, A., Jr., Azan, L., and Calviño, J. M.: Simultaneous tachycardias, Am. Heart J. **59**:358, 1960.
15. Palmer, R., and White, P. D.: Paroxysmal ventricular tachycardia with rhythmic alternation in the direction of the ventricular complexes of the electrocardiogram, Am. Heart J. **3**:454, 1928.
16. Bellet, S.: Clinical disorders of the heart beat, Philadelphia, 1953, Lea & Febiger.
17. Gobley, M., Ladopulos, C. P., Roth, F. H., and Scherf, D.: Changes of ventricular impulse formation during carotid pressure in man, Circulation **10**:735, 1954.
18. Scherf, D., Schott, A., Reid, E. C., and Chamsai, D. G.: Intermittent parasystole, Cardiologia **30**:217, 1957.
19. Castellanos, A., Calviño, J. M., Azan, L., and Castellanos, A., Jr.: Supraventricular tachycardia imitating ventricular paroxysmal tachycardia in infancy, J. Pediat. **54**:330, 1959.
20. Gaskell, W. H.: On the innervation of the heart, with special reference to the heart of the tortoise, J. Physiol. **4**:43, 1833.
21. Lewis, T., and Levy, R.: Heart irregularities, resulting from the inhalation of low percentages of chloroform vapour and their relation to ventricular fibrillation, Heart **3**:99, 1911-12.
22. Reid, W. D.: Ventricular ectopic tachycardia complicating digitalis therapy, Arch. Int. Med. **33**:23, 1924.

The central circulating blood volume in normal subjects and patients with mitral stenosis

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Measurement of the central circulating blood volume by the Stewart-Hamilton method has become routine in most hemodynamic studies in which cardiac output is determined by arterial dilution techniques. Although the simplicity of calculating this volume has resulted in the accumulation of a plethora of data, the physiologic significance of such determinations is obscure. A major limitation to physiologic meaningfulness is related to the time boundaries of such measurements of volume and to errors inherent in the use of peripheral arterial sampling sites.[1,2] The use of the central circulating blood volume as an estimate of pulmonary blood volume requires the closest approximation possible to the time boundaries of the lung, excluding the peripheral venous and arterial systems. Although such conditions can be most closely approximated by injection into the pulmonary artery and sampling from the left heart or aortic root, the practical limitations of these methods for general clinical use are apparent. The use of dilution curves recorded over the precordium for the determination of central circulating blood volume, as introduced by Shipley[3] and further elaborated by Lammerant,[4] offers a method whose time boundaries exclude systemic arteries and veins and which obviates catheterization procedures.

The intent of our study was to measure the central circulating blood volume by using the time boundary advantage of the precordial dilution technique, both in normal subjects and in patients with mitral stenosis. Since previous studies of this volume using peripheral sampling sites in patients with mitral stenosis have shown no measurable increase over normal,[5-7] the possibility of unmasking an increment in pulmonary blood volume was offered by the use of more meaningful time boundaries. A collateral objective was the measurement of the central circulating volume after exercise by a method uninfluenced by variations in flow at systemic arterial sampling sites. Although Lammerant[4] has used the precordial method extensively in both normal subjects and patients with mitral stenosis, exercise study of the central blood volume by this method in the latter group has not been made.

Method

The experimental groups consisted of 25 subjects without heart or lung disease, and 14 patients with mitral stenosis. Mitral stenosis in the latter group was predominant and "pure" in so far as could be documented by left atrial catheterization or subsequent mitral commissurotomy; none of the patients were in overt right heart failure at the time of the study, but the

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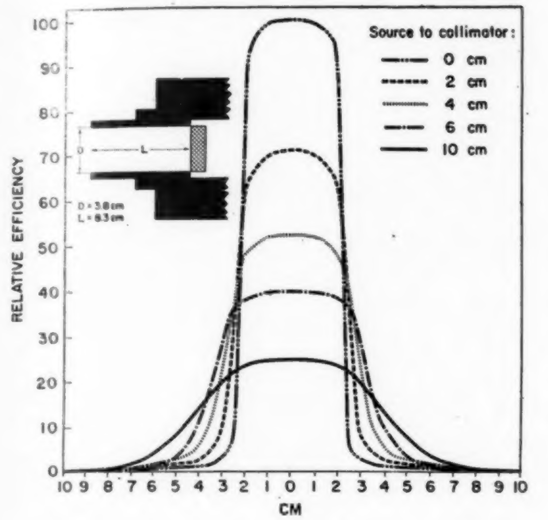

Fig. 1. The geometric characteristics of the collimator used in the study. Lead thickness of distal end of the collimator is 1 cm.

majority had clinical evidence of pulmonary hyperemia. All subjects were studied in the postabsorptive state without sedation. Eight of the normal subjects and a similar number of patients with mitral stenosis were studied before and immediately after the completion of the standard Master two-step exercise tolerance test.[8]

The determination was made with the patient comfortably seated in a special chair with adjustable arms.[9] Injections of 10 to 100 μc of I^{131} human serum albumin were made into a median basilic vein of the elevated right arm via an indwelling No. 18 Cournand needle; the isotope was contained in a volume of 2 to 3 ml. and was followed by a 10-ml. saline flush. Those subjects who were exercised were immediately reseated at the completion of the tolerance test, and the injection of isotope was made within 30 seconds of completion of the stress. All of the patients with mitral stenosis noted dyspnea at the completion of the exercise, and 2 were unable to complete the test.

The precordially placed detection device consisted of a 1½ inch sodium iodide scintillation crystal with attached photomultiplier tube; mounted in series with this device was a decimal scaler, counting rate computer, and a pen-writing Esterline Angus recording meter. The scintillation counter was shielded by a collimator, the geometric relationships of which were previously determined by a phantom radioactive source (Fig. 1). Since double-peaked curves were necessary to calculate mean circulation time between right and left heart, optimal counter placement for this type of tracing has been determined by previous studies in this laboratory.[9] In the determinations of the present study, small (5 to 10 μc) preliminary injections of the isotope were made in order to verify an optimum counter position for double-peaked curves. The best precordial site for securing such curves with our collimator has been along the left sternal border over the fifth or sixth ribs (Fig. 2).

Representative dilution curves recorded on semilogarithmic chart paper after the intravenous injection of 20 μc of I^{131} serum albumin in a normal subject and in a patient with mitral stenosis are shown in Fig. 3. Not all curves showed as discrete double peaks as in this illustration; such curves were discarded, and only those tracings in which clear-cut exponential disappearance was apparent or could be reconstructed were used in this study. From these double-peaked curves, cardiac output and mean circulation time between right and left heart were calculated for measurement of central circulating blood volume, using the Stewart-Hamilton equa-

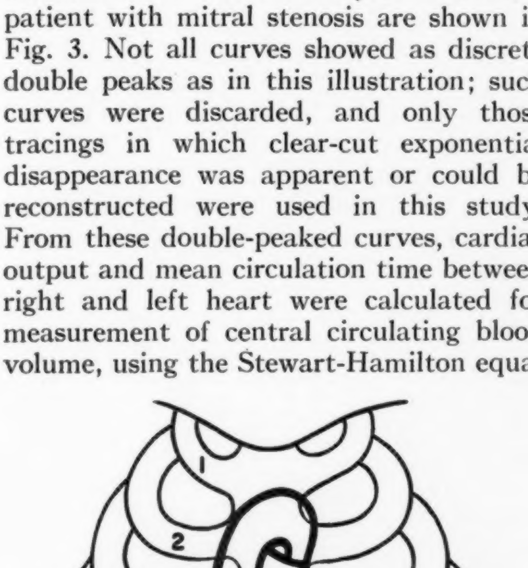

Fig. 2. Schematic projection of heart on chest wall. Cross-hatched area along the left sternal border indicates optimal site for double-peaked curves. Other shaded areas give predominant right or left curves.

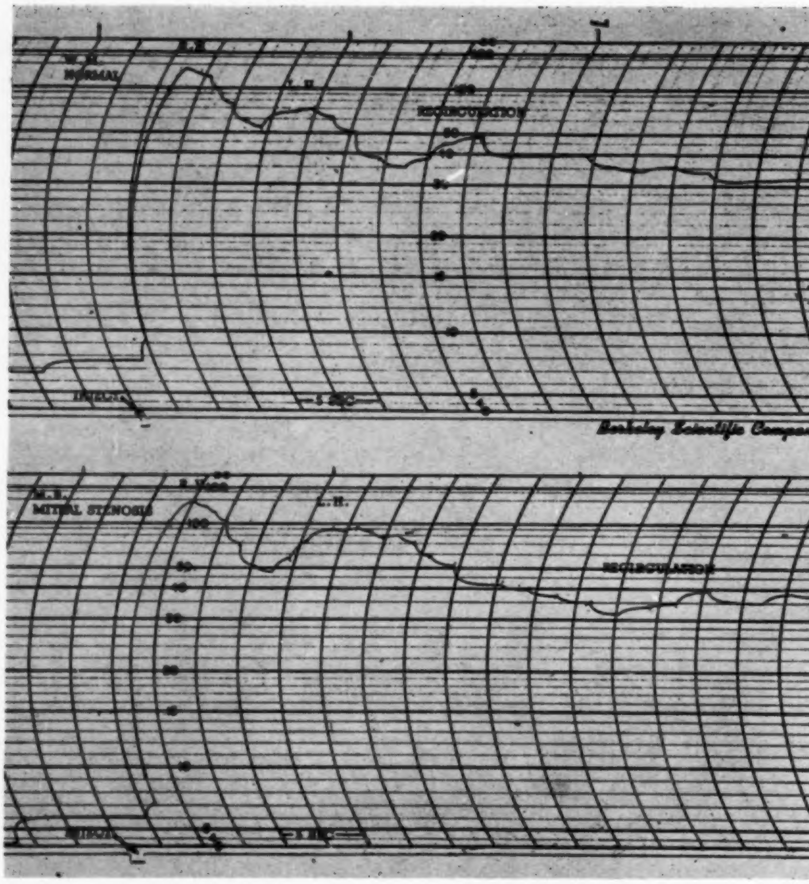

Fig. *3.* Representative dilution curves as recorded directly on logarithmic paper. Paper speed, 12 inches per minute. *Above:* Normal subject. *Below:* Patient with mitral stenosis.

tion, *Central Blood Volume (ml.) = Cardiac Output (ml./sec.)* × *Mean Transit Time (sec.)*. The mathematical methods used for curve analysis and calculation of these parameters were similar to those of Shipley[3] and Lammerant.[4] More recently, we have devised a mathematical method of biphasic dilution curve analysis that has simplified the calculation of cardiac output and mean transit time.[10] The time boundaries of this calculated blood space include half of the right heart, the lungs, and half of the left heart. Total blood volume was determined by the in vitro counting of a sample of whole blood obtained from the patient 10 minutes after the completion of each determination of output.

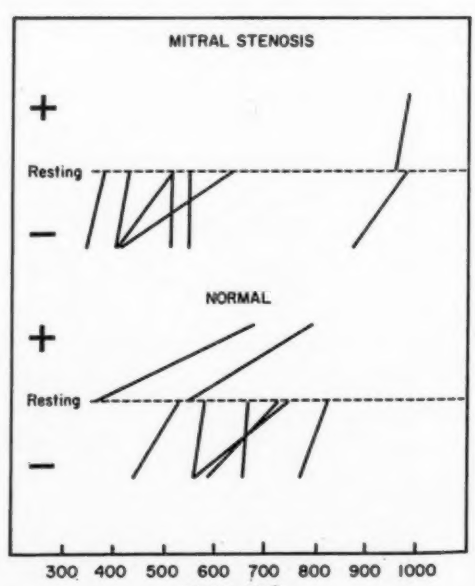

Fig. *4.* Directional change of central blood volume from resting after standard exercise in normal subjects and patients with mitral stenosis.

Results

Resting. Table I summarizes the mean values for central circulating blood volume and the associated parameters for its de-

termination in the normal subjects and in the patients with mitral stenosis. Although the mean value for the central volume expressed either as a function of body surface area or as a percentage of total blood volume is greater in the patients with mitral stenosis (678 ml./M.^{2}; 27 per cent of total blood volume) than in the normal subjects (610 ml./M.^{2}; 23 per cent of total blood volume), this difference is not statistically significant. The cardiac index is significantly higher and the mean transit time significantly shorter in the normal subjects than in the patients with mitral stenosis. The mean total blood volume is the same in both groups.

Exercise. The values for central blood volume, cardiac output, and mean transit time before and after exercise are shown in Tables II and III.

In the 8 normal subjects, in spite of significant elevations of cardiac output and decreases of mean transit time, the mean central circulating blood volume shows no change after exercise (620 ml./M.^{2} before, and 628 ml./M.^{2} after exercise; 25 per cent of total blood volume in both instances).

Similarly, the patients with mitral stenosis were able to effect an increase in cardiac output and decrease in mean transit time after exercise but showed a decrease in the mean value for central volume (618 ml./M.^{2} before, and 560 ml./M.^{2} after exercise; 24 and 21 per cent of total blood volume before and after exercise, repectively). However, this decrease in central volume is not significant in the small sample tested.

Total blood volume showed a slight rise after exercise in both groups, but the increments were not significant: 69 ± 8 ml./Kg. before, to 71 ± 9.9 ml./Kg. after exercise in normal subjects; and 73 ± 11.4 ml./Kg. before, to 75 ± 10.4 ml./Kg. after exercise in the patients with mitral stenosis.

Although in both groups the *mean* value for central volume showed no significant change after exercise, there were individual variations, as illustrated in Tables II and III and Fig. 4. It is noteworthy, however, that among the normal subjects and the patients with mitral stenosis the majority showed either no change or a decrease in central volume after the exercise test. In 2 normal subjects (C. E. and W. B., Table II) and one patient with mitral stenosis (H. D., Table III) the increase in calculated central volume after exercise was largely due to a relatively small decrease in mean transit time as compared to the findings in the majority of individuals studied. There were no other distinctive clinical or hemodynamic features in these 3 subjects.

All of the normal subjects and the patients with mitral stenosis showed a rise in cardiac output after exercise, together with a decrease in mean circulation time. However, the mean increment in cardiac output was significantly greater in normal subjects than in the patients with mitral stenosis.

Table I. ***Comparison summary of mean values for central circulating blood volume and associated parameters at rest in normal subjects and patients with mitral stenosis***

	Cardiac index ($L./M.^2/min.$)	Mean transit time (sec.)	Central blood volume		Total blood volume (ml./Kg.)
			ml./M.^{2}	% total blood volume	
Normal subjects (25)	3.30	11.1	610	23	71.0
S.D.	±0.53	±2.5	±168	±5.9	±10.2
Patients with mitral stenosis (14)	2.57	15.8	678	27	72.0
S.D.	±0.58	±3.3	±190	±6.0	±9.8
t	4.05	4.98	1.14	1.95	0.30
p	<0.01	<0.01	0.2	>0.05	>0.5

Discussion

The theory and mathematical analysis of biphasic, precordial dilution curves for measurement of cardiac output, mean transit time, and central circulating blood volume has been reported *in extenso* by Lammerant,[4] and by our laboratory.[9-11] This technique has also been recently applied clinically by Eich[12] and by Love[13] in the determination of central volume in normal subjects and in patients with heart disease. The major advantages of the precordial method are its simplicity of application, obviating both cardiac catheterization and arterial puncture, and the attainment of central blood volume boundaries excluding the peripheral venous and arterial circulations. The exclusion of peripheral arterial sampling sites makes possible the study of the central blood volume after various stresses (exercise, drugs) uninfluenced by redistribution of arterial flow. The limitations of this technique for the measurement of cardiac output and circulation time as mentioned by Shipley[3] for wide-angle counting have been improved upon by the use of well-collimated precordial counters and by the measurement of *mean* transit time rather than *peak to peak* times.

The failure of the present study to demonstrate a clear-cut increase in central blood volume in patients with mitral stenosis over that in normal subjects parallels the experience of Lammerant,[4] using the same technique, and is similar to other dilution studies using peripheral sampling sites.[5-7] The enigma presented is that of a normal central blood volume in the face of clinical evidence of cardiomegaly and pulmonary hyperemia. One group of investigators has speculatively derived the hypothesis that in the presence of a normal central volume and an enlarged heart the pulmonary component of this volume must be less than normal in mitral stenosis.[14] On the other hand, another group has found an increase in central blood volume if this volume is related to cardiac output[15]; however, the ratio of central volume to cardiac output proposed by them appears to be a tautology and merely indicates that the mean transit time is prolonged in mitral stenosis. Rapaport[7] suggested that the normal central volume in mitral stenosis is due to low cardiac output, and presented preliminary data to show an increase in this volume when the output was increased by exercise. Similarly, Ball[14] has reported an increase in central blood volume after exercise in a group of patients with mitral stenosis. However, in both of these studies the central blood volume was calculated from dilution curves recorded at peripheral arterial sampling sites. Our study does not demonstrate that central volume is dependent on cardiac output in cases of mitral stenosis. All 8 of our patients had increases in cardiac output with either a decrease or no significant change in the calculated central volume.

We believe that the failure to find an increase in central blood volume in the face of the pulmonary congestion and cardiomegaly of mitral stenosis may represent a limitation of the Stewart-Hamilton dilution technique. Although by this method Schlant[16] has found a good correlation of the calculated central blood volume with a total central blood space measured by Cr^{51}-tagged erthyrocytes, these studies were made in dogs with noncongested lungs and normal-sized hearts. A critical study of this type pertinent to pulmonary hyperemia and cardiomegaly has not as yet been made. Until data to the contrary are available, we would speculate that in the presence of pulmonary congestion a time-concentration dilution curve, although giving a reliable estimate of cardiac output, fails to measure a mean transit time representative of the total pulmonary blood volume because of the inability of the tracer material to penetrate into slow-moving or stagnant blood spaces during the primary circulation through the lung. To the extent that the calculated volume is accepted as a *circulating* volume,[17] it is appropriately and usefully studied. However, the measurement of *total* central blood volume and its major component of interest, the lung, is probably not amenable to the application of the Stewart-Hamilton method in situations of pulmonary congestion.[18] An equilibration method of estimation of pulmonary blood volume seems more appropriate. Such a technique has been used,[7] but objections relative to its application in the high-flow, low-volume space of the lung have been raised.[19]

Like Lammerant,[4] we found that the majority of the normal subjects had elevation of cardiac output after exercise without an increase in central blood volume. Lammerant, in fact, demonstrated a significant lowering of central volume after exercise with this technique. These demonstrations of increased cardiac output without an increase in calculated central volume are discordant with exercise studies in which

Table II. *Values for central circulating blood volume and associated parameters before and after exercise in normal subjects*

Patient	Cardiac index (L./M.²/min.)			Mean transit time (sec.)			Central blood volume: ml./M.²			Central blood volume: % total blood volume		
	Rest	Exercise	Change	Rest	Exercise	Change	Rest	Exercise	Change	Rest	Exercise	Change
J.R.	2.90	5.80	+2.90	15.7	5.8	−9.9	745	560	−185	31.0	23.0	−8.0
H.P.	3.16	3.98	+0.82	13.8	8.8	−5.0	725	582	−143	27.0	21.0	−6.0
C.E.	3.25	5.58	+2.33	10.1	8.5	−1.6	543	790	+247	23.0	37.0	+14.0
A.Z.	3.73	4.20	+0.47	8.5	6.3	−2.2	528	437	−91	18.0	14.0	−4.0
J.W.	3.42	6.40	+3.00	11.6	6.1	−5.5	664	650	−14	26.0	24.0	−2.0
J.F.	3.14	4.45	+1.31	15.8	10.3	−5.5	820	765	−55	36.0	32.0	−4.0
W.B.	2.10	4.05	+1.95	10.3	10.0	−0.3	362	675	+313	16.0	27.0	+11.0
A.Y.	3.80	5.50	+1.70	9.1	6.2	−2.9	576	568	−8	22.0	21.0	−1.0
Mean	3.18	5.00	+1.82	11.8	7.7	−4.1	620	628	+8	25.0	25.0	0.0
S.D.	±0.58	±0.93		±2.9	±1.9		±145	±116		±6.6	±7.2	
% Change			+57			−35			+1			0.0
t			4.76			3.36			1.18			0.916
p			<0.01			<0.01			>0.2			>0.2

Table III. *Values for central circulating blood volume and associated parameters before and after exercise in patients with mitral stenosis*

Patient	Cardiac index (L./M.²/min.)			Mean transit time (sec.)			Central blood volume: ml./M.²			Central blood volume: % total blood volume		
	Rest	Exercise	Change	Rest	Exercise	Change	Rest	Exercise	Change	Rest	Exercise	Change
R.D.	1.70	2.22	+0.52	13.2	9.4	−3.8	380	344	−36	17.0	16.0	−1.0
L.T.	2.12	3.40	+1.28	14.4	9.0	−5.4	512	510	−2	23.0	21.0	−2.0
M.B.	2.00	2.15	+0.15	15.4	11.2	−4.2	517	406	−111	22.0	15.0	−7.0
J.E.	2.80	4.60	+1.80	11.5	7.1	−4.4	546	545	−1	21.0	20.0	−1.0
M.G.	3.10	4.60	+1.50	12.4	5.7	−6.7	640	407	−233	29.0	18.0	−11.0
P.W.	3.70	5.00	+1.30	15.7	10.4	−5.3	978	870	−108	28.0	26.0	−2.0
H.D.	3.20	3.90	+0.70	17.7	14.8	−2.9	955	975	+20	33.0	34.0	+1.0
L.M.	2.20	3.10	+0.90	12.0	7.7	−4.3	428	405	−23	18.0	18.0	0.0
Mean	2.60	3.62	+1.02	14.0	9.4	−4.6	618	560	−58	24.0	21.0	−3.0
S.D.	±0.70	±1.09		±2.1	±2.8		±226	±234		±5.6	±6.2	
% Change			+38			−34			−10			−13
t			2.23			3.68			0.52			0.98
p			<0.05			<0.01			>0.5			>0.5

peripheral arterial sampling sites have been used.[20,21] However, it has been convincingly demonstrated that arterial redistribution after exercise may give spuriously high estimates of mean transit time for the calculation of the central volume with the use of peripheral sampling sites.[1,22] Exercise studies, on the other hand, using aortic root sampling have shown elevations of cardiac output three times greater than resting values without an increase in calculated central blood volume.[23] The precordial dilution technique approximates the conditions of aortic root sampling and may give a better estimation of actual central circulating blood volume after exercise than do peripheral sampling methods.

Summary

A precordial dilution method for the measurement of the central circulating blood volume has been used in a group of normal subjects and in patients with predominant mitral stenosis. This technique obviates arterial puncture and cardiac catheterization, and has the advantage of mean transit time boundaries confined to the heart and lungs.

In the resting state no significant difference in central blood volume was found between the normal subjects and the patients with mitral stenosis. This finding has prompted a tentative conclusion that the Stewart-Hamilton dilution method for determination of the central blood volume may be inappropriate in situations of pulmonary congestion.

Determinations of central blood volume were also made in normal subjects and in patients with mitral stenosis after a standard exercise test. No dependence of the central volume on cardiac output was demonstrated in either group, nor was the ability to increase cardiac output after exercise directly related to the calculated central blood volume.

REFERENCES

1. Gleason, W. L., Bacos, J. M., Miller, D. E., and McIntosh, H. D.: A major pitfall in the interpretation of the central blood volume, Clin. Res. **7**:227, 1959.
2. Marshall, R. J., Wang, Y., and Shepherd, J. T.: Components of the "central" blood volume in the dog, Circulation Res. **8**:93, 1960.
3. Shipley, R. A., Clark, R. E., Liebowitz, D., and Dromer, J. S.: Analysis of the radiocardiogram in heart failure, Circulation Res. **1**:428, 1953.
4. Lammerant, J.: Le volume sanguine des poumons chez l'homme, Bruxelles, 1957, Editions Arscia.
5. Borden, C. W., Ebert, R. V., Wilson, R. H., and Wells, H. S.: II. The circulation time from the pulmonary artery to the femoral artery and the quantity of blood in the lungs in patients with mitral stenosis and in patients with left ventricular failure, J. Clin. Invest. **28**:1138, 1949.
6. Kopelman, H., and Lee, G.: The intrathoracic blood volume in mitral stenosis and left ventricular failure, Clin. Sc. **10**:383, 1951.
7. Rapaport, E., Kuida, H., Haynes, F. W., and Dexter, L.: The pulmonary blood volume in mitral stenosis, J. Clin. Invest. **35**:1393, 1956.
8. Ford, A. B., and Hellerstein, H. K.: Energy cost of the Master two-step test, J.A.M.A. **164**:1868, 1957.
9. Pritchard, W. H., MacIntyre, W. J., and Moir, T. W.: The determination of cardiac output by the dilution method without arterial sampling. II. Validation of precordial recording, Circulation **18**:1147, 1958.
10. Gott, F. S., Moir, T. W., MacIntyre, W. J., and Pritchard, W. H.: A mathematical model for dilution curves for flow study, Circulation Res. (In press.)
11. MacIntyre, W. J., Pritchard, W. H., and Moir, T. W.: The determination of cardiac output by the dilution method without arterial sampling. I. Analytical concepts, Circulation **18**:1139, 1958.
12. Eich, R. H., Chaffee, W. R., and Chodos, R. B.: Measurement of central blood volume by external monitoring, Circulation **20**:689, 1959.
13. Love, W. D., O'Meallie, L. P., and Burch, G. E.: Estimation of the volume of blood in the right heart, left heart and lungs in intact man by radioisotope technics, Circulation **20**:731, 1959.
14. Ball, J. D., Kopelman, H., and Witham, A. C.: Circulatory changes in mitral stenosis at rest and on exercise, Brit. Heart J. **14**:363, 1952.
15. Braun, K., Rosenberg, S. Z., and Schwartz, A.: Central blood volume, cardiac output, and pulmonary vascular pattern in mitral stenosis, Am. J. Cardiol. **3**:40, 1959.
16. Schlant, R. C., Novack, P., Kraus, W. L., Moore, C. B., Haynes, F. W., and Dexter, L.: Determination of central blood volume. Comparison of Stewart-Hamilton method with direct measurement in dogs, Am. J. Physiol. **196**:499, 1959.
17. Hamilton, W. F., Moore, J. W., Kinsman, J. M., and Spurling, R. G.: Simultaneous determination of the greater and lesser circulation times, of the mean velocity of blood flow through the heart and lungs, of the cardiac output and an approximation of the amount of blood actively circulating in the heart and lungs, Am. J. Physiol. **85**:377, 1928.
18. Meier, P., and Zierler, K. L.: On the theory of the indicator dilution method for measurement of blood flow and volume, J. Appl. Physiol. **6**:731, 1954.

19. Braunwald, E., Fishman, A. P., and Cournand, A.: Estimation of volume of a circulatory model by the Hamilton and the Bradley methods at varying flow volume ratios, J. Appl. Physiol. 12:445, 1958.
20. Mitchell, J. H., Sproule, B. J., and Chapman C. B.: The physiological meaning of the maximal O_2 uptake test, J. Clin. Invest. **37**:538, 1958.
21. Braunwald, E., and Kelly, E. R.: The effects of exercise on central blood volume in man, J. Clin. Invest. **39**:413, 1960.
22. Marshall, R. J.: Significance of changes in "central" blood volume in man during exercise, Fed. Proc. **19**:118, 1960.
23. Semler, J., Shepherd, J. T., and Marshall, R. J.: Pressure-flow-volume relationships in the pulmonary circulation of the exercising dog, Fed. Proc. **18**:141, 1959.

The use of intracardiac carbon dioxide in the diagnosis of pericardial disease

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This preliminary report offers confirmation of and support for the work of previous investigators demonstrating the safety and diagnostic value of intracardiac carbon dioxide in negative-contrast roentgenography. Durant, Oppenheimer, Stauffer and colleagues[1-4] developed the method and demonstrated its diagnostic value. Scatliff, Kummer and Janzen[5] recently reported on the application of this method in a series of 22 patients. The greatest value of the procedure thus far has been its use in the differentiation of the "large heart" of myocardial dilatation from that of pericardial disease and effusion.

With a patient in the left lateral decubitus position, carbon dioxide, once in the right atrium, will rise and outline the right lateral limits of this cardiac cavity while forming a gas-blood interface below. These events are demonstrated by roentgenography. One observes from the patient's right to left the aerated lungs, the opaque right atrial wall or "band," the bubble of carbon dioxide, and the blood level. The right atrial wall or "band" is composed of visceral and parietal pleura, parietal and visceral pericardium, and right atrial myocardium and endocardium. In myocardial dilatation the right atrial "band" shows little if any change in width. Because of the relationships of specific gravity in free pericardial effusion, the heart assumes a dependent position, and the right atrial "band" is widened by the pericardial fluid. Some widening of this area may be seen in acute or chronic pericarditis without effusion, but here the widening is frequently not so great, and, in addition, other clues help to distinguish this from significant pericardial effusion.

Materials and methods

The materials necessary for this procedure are demonstrated in Fig. 1. They consist of: (1) sterile 18-gauge needle; (2) sterile plastic extension tube; a P-10 Sterilon expendible plastic tube was used; (3) sterile three-way stopcock; (4) sterile 50-c.c. or 100-c.c. syringe; (5) sterile 20-c.c. syringe with normal saline; (6) suitable tubing for connection between the stopcock and the tank of carbon dioxide; the rubber tubing and glass adaptor from a routine hospital intravenous fluid set has been found to be perfectly acceptable; (7) tank

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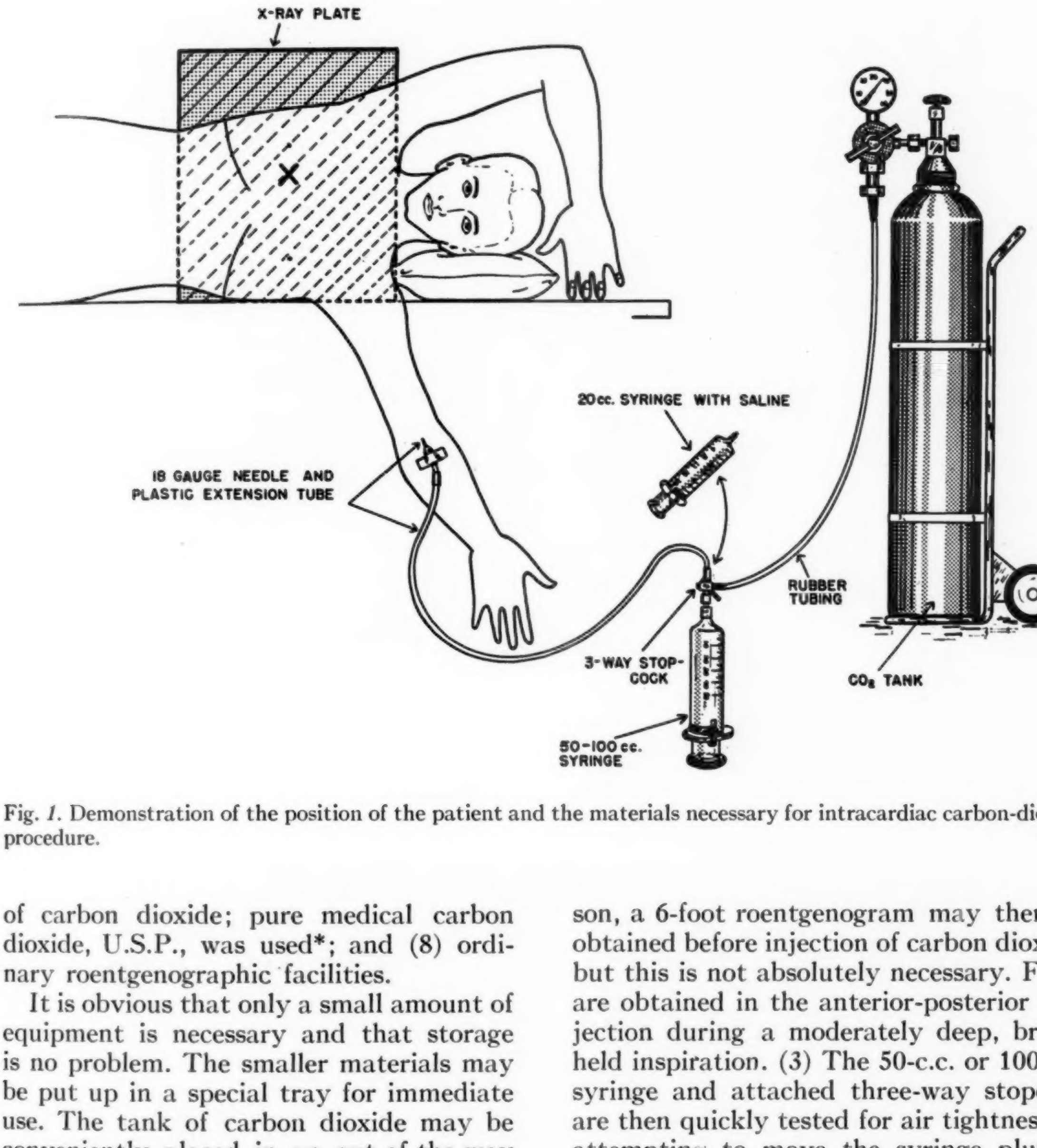

Fig. *1*. Demonstration of the position of the patient and the materials necessary for intracardiac carbon-dioxide procedure.

of carbon dioxide; pure medical carbon dioxide, U.S.P., was used*; and (8) ordinary roentgenographic facilities.

It is obvious that only a small amount of equipment is necessary and that storage is no problem. The smaller materials may be put up in a special tray for immediate use. The tank of carbon dioxide may be conveniently placed in an out-of-the-way corner of the x-ray room.

For purposes of simplicity the procedure recommended by others was modified. The procedure is as follows. (1) As shown in Fig. 1, the patient is placed in the left lateral decubitus position (right side up) on a suitable table in front of the 14-by-16 roentgenographic film. A vein in the antecubital region of the left arm is entered with the 18-gauge needle, which is attached to the plastic extension tube and the 20-c.c. syringe filled with 0.85 per cent NaCl. The needle is kept open by periodic injections of the saline. (2) For later comparison, a 6-foot roentgenogram may then be obtained before injection of carbon dioxide, but this is not absolutely necessary. Films are obtained in the anterior-posterior projection during a moderately deep, briefly held inspiration. (3) The 50-c.c. or 100-c.c. syringe and attached three-way stopcock are then quickly tested for air tightness by attempting to move the syringe plunger while the sterile-gloved finger blocks the openings of the stopcock. Connection is then made to the tank of carbon dioxide, and the entire apparatus is "washed" several times with the carbon-dioxide gas by repeatedly filling and emptying the syringe. (4) The empty 50-c.c. or 100-c.c. gas syringe and the attachments that have been washed with the carbon dioxide are then connected by the stopcock to the plastic extension tube after removal of the 20-c.c. syringe. (5) The x-ray technician is then alerted, the syringe filled with the desired amount of carbon dioxide, the stopcock turned, and the gas injected intravenously as rapidly as possible. We have

*Supplied by the National Gas Company, Medical Gas Division, Chicago, Ill. (tank type G, contents 3,200 gallons).

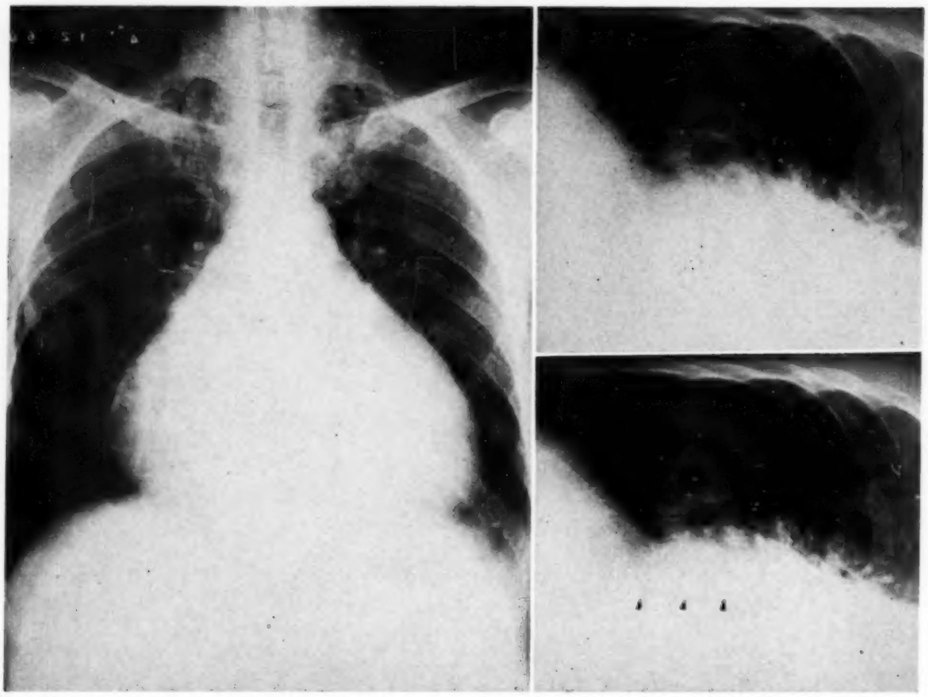

Fig. 2. Patient No. 1. *Left:* Teleoroentgenogram, showing markedly enlarged cardiac shadow and bilateral apical pulmonary infiltrates. *Upper right:* Preinjection film. *Lower right:* Postinjection film, showing bubble of carbon dioxide deep in the cardiac shadow (*arrows*). The right atrial band measures 41 mm. in width.

Fig. 3. Patient No. 1. *Left:* Lateral decubitus, showing air in pericardial sac. The thickened pericardium measures 17 mm. in width. *Right upper and lower:* After injection of carbon dioxide at 4 and 8 seconds, respectively, showing air in pericardial sac, *above*, and carbon dioxide in right atrium and cavae, *below*.

used 50 to 100 c.c. of gas (approximately 1 c.c. per kilogram) but have found that 50 c.c. is usually suitable. (6) The postinjection roentgenogram is then made. We obtained films immediately, 4 seconds, 8 seconds, and 15 seconds after the completion of the injection, but a single film at 4 seconds has proved satisfactory. (7) The patient is then maintained in the left lateral decubitus position for at least 10 minutes after the injection of the carbon dioxide, in order to insure complete absorption of the gas from the right atrium.

The entire operation requires only a few minutes. The procedure is useful, safe, simple, and causes no distress to the patient. The noise of the gas entering the vein is clearly audible, and, with the stethoscope, one may easily detect "gurgling" sounds due to the gas in the heart.

To date the procedure has been employed 36 times in 25 patients in this laboratory.

Case reports

Patient No. 1. S. R., a 49-year-old Negro man, was admitted to Charity Hospital with a history of several months of low-grade fever, malaise, and loss of weight. For 4 to 5 days prior to admission, there had been slight dyspnea and moderate pain in the lower substernal region of the chest. A teleoroentgenogram revealed a markedly enlarged heart shadow and bilateral apical pulmonary infiltration, more prominent on the right (Fig. 2). Shortly after admission a carbon-dioxide study showed a flattened gas bubble deep in the heart shadow (Fig. 2). Three days later a diagnostic pericardial paracentesis was done, and 200 to 300 c.c. of cloudy yellow fluid was removed, followed by instillation of 30 c.c. of air in the pericardial sac. A roentgenogram then revealed an air-fluid level below a thickened shaggy pericardium (Fig. 3). A repeat carbon-dioxide study was done and again showed the bubble of carbon dioxide deep in the heart shadow in the right atrium and venae cavae, plus the air bubble in the pericardial sac (Fig. 3). Subsequent cultures of the pericardial fluid were positive for tuberculosis.

Patient No. 2. J. T., a 47-year-old Negro man, was admitted to Charity Hospital because of findings suggestive of right and left ventricular congestive failure and a definitely enlarging cardiac shadow on repeated outpatient chest x-ray films during the preceding year. He was a chronic alcoholic who gave a very unreliable history. There were records of several previous admissions for knife wounds of the chest; on one occasion 2 years previously this was associated with hemopericardium. The possibility of chronic pericarditis was raised, but subsequent carbon-dioxide study revealed a thin right atrial band with rounded, unflattened contour (Fig. 4).

Patient No. 3. E. C., a 43-year-old Negro woman with a clinical diagnosis of postpartal myocarditis, had been followed up for the preceding 2 years. There had been repeated episodes with findings of

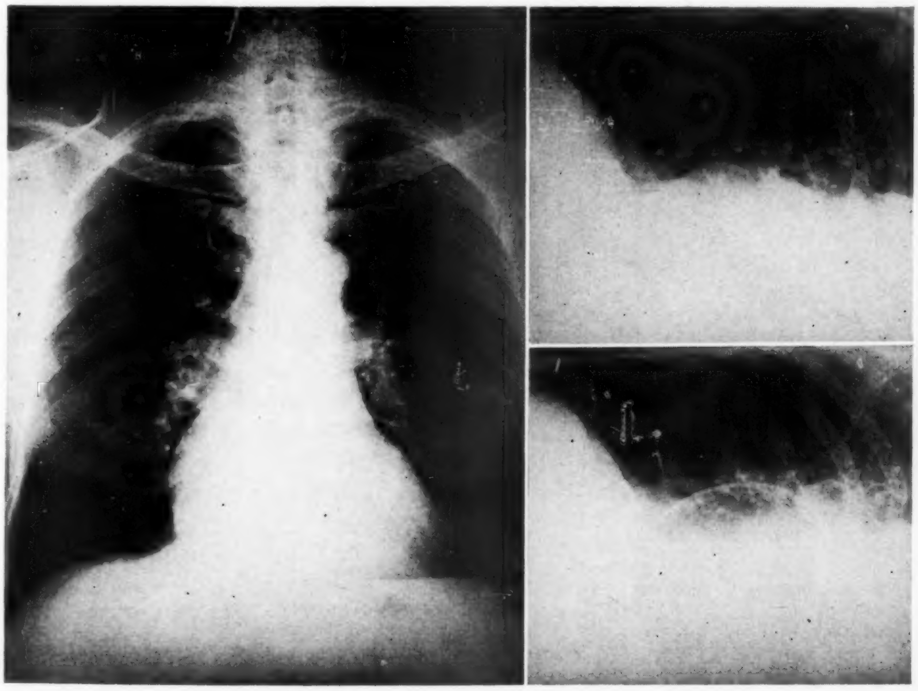

Fig. *4*. Patient No. 2. *Left:* Teleoroentgenogram, showing mild to moderate cardiomegaly. *Upper right:* Preinjection film. *Lower right:* Postinjection film, showing thin right atrial band (2-3 mm.) with rounded, unflattened contour.

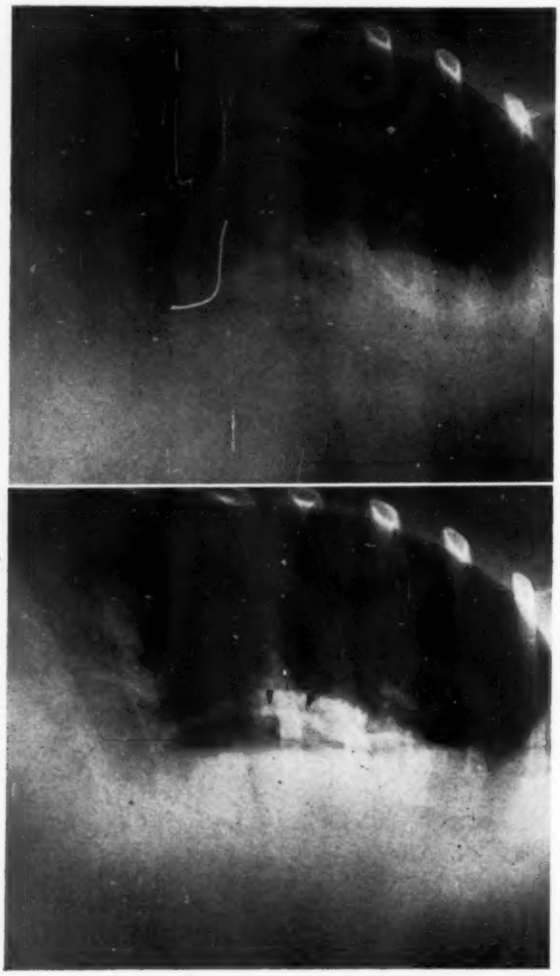

Fig. 5. Patient No. 3. *Upper:* Preinjection film. *Lower:* Postinjection film, showing gas in right atrium, cavae, and right atrial appendage (*arrows*). The right atrial band at its inferior arc measured 4 mm.

left, but especially right, ventricular failure. Because of a globular heart shadow on x-ray examination, the possibility of pericardial effusion was raised. Carbon-dioxide study, however, revealed a normal right atrial band, compatible with myocardial dilatation rather than effusion (Fig. 5). The films were interesting in that gas trapped in the right atrial appendage could be identified.

Patient No. 4. L. W., a 33-year-old Negro woman, was admitted to Charity Hospital with a 5-day history of fever, severe anterior chest pain, and dry hacking cough. The electrocardiogram was typical of acute pericarditis, and a teleoroentgenogram on admission revealed a moderately large heart shadow and bilateral slight pleural effusions (Fig. 6). A few days later, after 3 thoracenteses, little if any pleural fluids could be demonstrated roentgenographically. Injection of carbon dioxide revealed a uniform widening of the right atrial band (Fig. 6), suggestive of acute pericardial thickening, with little or no pericardial fluid. Nevertheless, since the etiological diagnosis was doubtful, several pericardial paracenteses were attempted on two different occasions. No pericardial fluid was obtained even though the needle touched the left ventricular wall several times. The subsequent clinical course of the patient was compatible with subsiding acute pericarditis.

Patient No. 5. C. L., a 15-year-old white girl, was admitted to Charity Hospital in a terminal clinical state with long-standing uremia from chronic glomerulonephritis. A teleoroentgenogram revealed a moderately enlarged heart (Fig. 7). Injection of carbon dioxide showed a somewhat flattened gas bubble deep in the cardiac shadow (Fig. 7). In addition, regurgitation of the gas into the hepatic veins was clearly demonstrated. Subsequent autopsy, 2 weeks later, revealed slight to moderate thickening of the pericardium and a few hundred cubic centimeters of pericardial fluid.

Patient No. 6. W. R., a 54-year-old Negro man, is included in this series because of special interest only. He had a classic clinical picture of obstruction of the superior vena cava due to mediastinal malignancy. Injection of carbon dioxide outlined the dilated superior cava and located the site of obstruction by the tumor mass (Fig. 8).

Discussion

The carbon-dioxide procedure is simple, quickly performed, and useful diagnostically. The procedure is safe and free from gas embolism because carbon dioxide is 20 times more soluble in blood than either oxygen or air. Even large doses of the gas (7.5 c.c. per kilogram) alter the carbon-dioxide content of blood by only 5 to 10 volumes per cent, and this is quite transient (1 to 2 minutes).[3] Change in blood pH is negligible.[3,5]

The carbon-dioxide cardiography provides essentially the same information as angiocardiography with radiopaque media, and there are no allergic reactions from the former. Cardiac catheterization has been advocated to substantiate suspected cases of pericardial effusion, but this procedure is much less practical and far more complicated and expensive. Injections of carbon dioxide may be employed safely and usefully in any institution with facilities for routine roentgenography. To date no adverse reactions to this procedure have been noted in this laboratory.

At present the prime indication for this procedure appears to be in patients with suspected pericardial effusion, especially in those in whom differentiation from myocardial dilatation is in doubt. The procedure also appears to be of value in both acute and chronic pericarditis, with

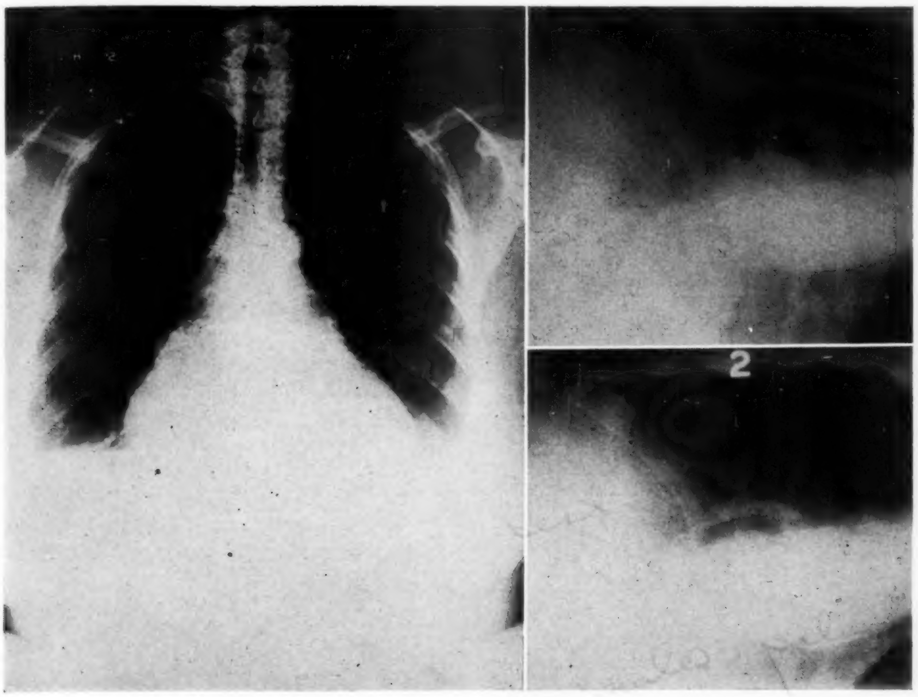

Fig. 6. Patient No. 4. *Left:* Teleoroentgenogram on admission, showing enlarged cardiac shadow and bilateral small pleural effusion. *Upper right:* Preinjection film taken several days later. *Lower right:* Postinjection film, showing carbon dioxide in right atrium and uniform thickening of right atrial band, measuring 11 mm. in width.

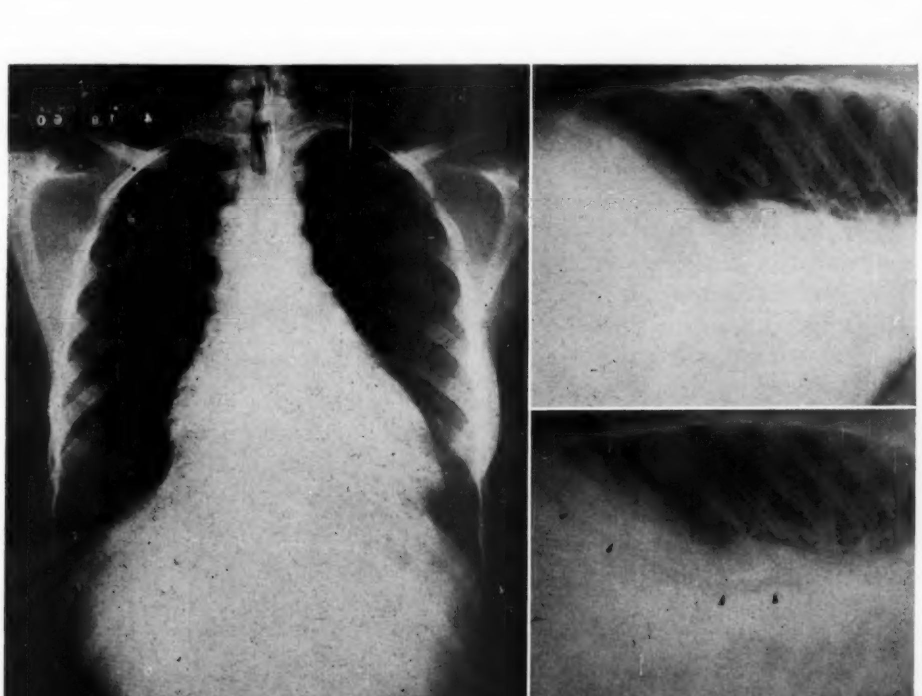

Fig. 7. Patient No. 5. *Left:* Teleoroentgenogram, showing enlarged cardiac shadow and calcified right paratracheal node. *Upper right:* Preinjection film. *Lower right:* Postinjection film, showing carbon dioxide deep in the cardiac shadow. Gas is noted to be regurgitating into hepatic veins.

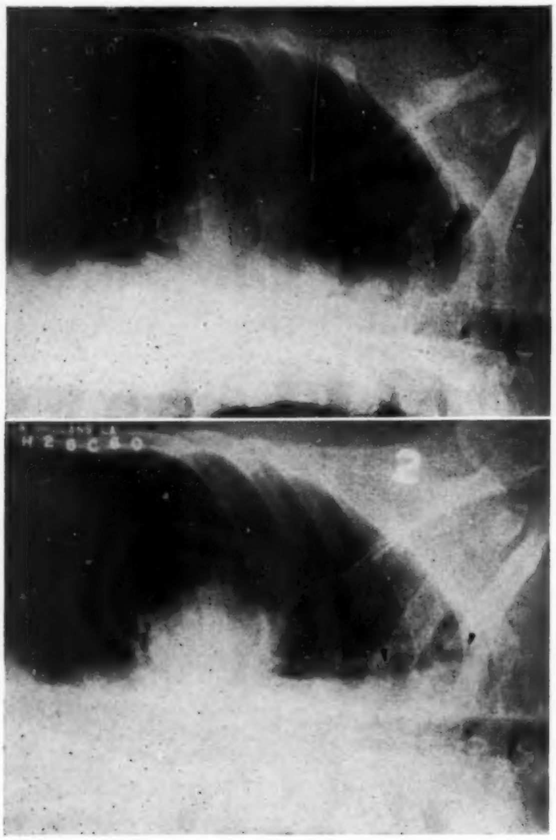

Fig. *8*. Patient No. 6. *Upper:* Preinjection film. *Lower:* Postinjection film, showing carbon-dioxide-filled superior vena cava (*arrows*) ending abruptly at mediastinal mass.

or without effusion. It can assist in the study of some vascular disturbances, such as obstruction to large veins, e.g., the superior vena cava. It possibly could assist with the detection of tumors of the right atrium. With larger doses of carbon dioxide it may help delineate disturbances in the right ventricular outflow tract.[3] Its value in man with intracardiac shunts and its value in the diagnosis of peripheral vascular lesions has yet to be demonstrated.

There are few contraindications. There is a possible contraindication in patients with intracardiac shunts because of the danger of gas embolization to the brain or coronary arteries should the gas reach the left side of the circulation. It has been demonstrated, however, that quite large amounts of carbon dioxide may be injected into the left ventricle of dogs with no adverse effects.[3] This danger is extremely unlikely in man lying on his left side. Appropriate caution is advised in patients with impaired mechanisms for carbon-dioxide excretion, such as in patients with far advanced pulmonary emphysema, because of the danger of provoking severe carbon-dioxide narcosis.[3]

One obvious contraindication exists in severely ill patients, such as patients with marked orthopnea who might be unable to maintain the left lateral decubitus position for the required length of time.

A few precautions are necessary in addition to those mentioned above. Of foremost importance is that *pure* carbon dioxide only be employed for injection. Some tanks of so-called hospital carbon dioxide contain significant amounts of oxygen. Purity of the gas should be thoroughly checked with the manufacturer or other responsible authorities. In one instance, gas supplied to this laboratory as "pure" carbon dioxide actually contained 4 per cent oxygen. As an extra precaution we have analyzed the gas from the tank ourselves before use.

From observations in this laboratory and from those of others,[1-5] several "patterns" may be recognized roentgenographically

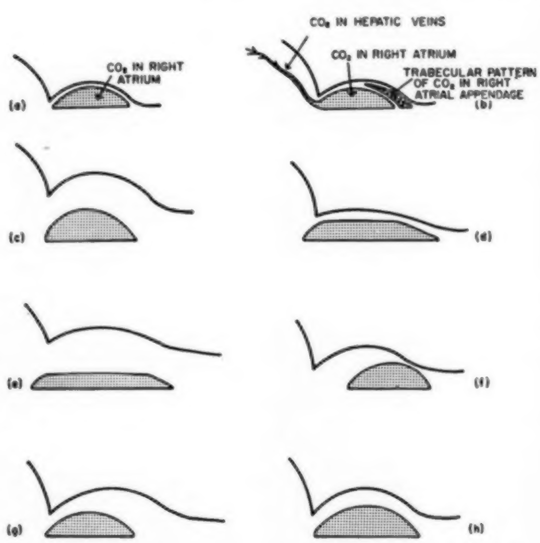

Fig. *9*. *a*, The normal right atrial band, as noted in Patients Nos. 2 and 3. *b*, The normal right atrial band plus carbon dioxide in right atrial appendage and in hepatic veins, as noted in Patients Nos. 3 and 5, respectively. *c*, The very thick right atrial band with upper convexity of gas bubble. *d*, Moderate to marked flattening of right atrial band. *e*, The very thick right atrial band, also showing moderate to marked flattening, as noted in Patient No. 1. *f* and *g*, Asymmetrical widening of the right atrial band. *h*, Uniform thickening of the right atrial band, with upper convexity of the gas bubble, as noted in Patient No. 4.

after intravenous injection of carbon dioxide. It should be stressed, however, that our observations on patients with the diagnoses proved absolutely by operation or autopsy have been limited, and the initial impressions may have to be modified in the future. Fig. 9 demonstrates several of these patterns.

The normal right atrial band. This band measures 5 mm. or less in width and is illustrated in Fig. 9,*a*. Patients Nos. 2 and 3 in our series are examples of the normal. At times, gas may be seen in the right atrial appendage or in the hepatic veins (Fig. 9,*b*), as noted in Patient No. 3 and No. 5, respectively. As seen in other illustrations, gas may be also detected in the inferior and superior venae cavae.

The very thick right atrial band, measuring greater than 20 mm. in width, with a rounded inferior border of the atrial band (Fig. 9,c). This is considered[5] to be diagnostic of at least some, but usually massive, pericardial effusion, with little if any chronic fibrotic pericardial change.

Moderate to marked flattening or straightening of the inferior surface of the right atrial band, with measurements less than 20 mm. (Fig. 9,d). This appears to be indicative of subacute or chronic pericardial thickening with diminished distensibility.[3-5] Superimposed effusion might be present.

Moderate to marked flattening or straightening of the inferior surface of the right atrial band, with widening greater than 20 mm. (Fig. 9,e). This is suggestive of chronic pericardial thickening plus pericardial effusion. This was demonstrated in Patient No. 1. It seems unlikely that acute or chronic pericardial thickening alone would result in widening of the atrial band to over 20 mm. in the absence of effusion.[5]

Asymmetrical thickening of the right atrial band, measuring 5 to 20 mm. at its widest (Fig. 9,f and g). This is highly suggestive of pericardial effusion, with asymmetrical distribution of the fluid over the right atrium.[5]

Uniform thickening of the right atrial band, measuring 5 to 20 mm. in width, with a rounded superior border of the gas bubble (Fig. 9,h). This is suggestive of acute pericardial thickening with little superimposed effusion. This was present in Patient No. 4.

One note of caution in interpretation lies in the problem met with when a patient presents with a right pleural effusion. In such cases, when the patient lies in the left lateral decubitus position, pleural fluid may gravitate down over the right cardiac border and simulate intrapericardial fluid on the carbon-dioxide roentgenogram. Here one frequently must wait until the fluid disappears spontaneously or is removed after thoracentesis before proceeding with the carbon-dioxide study.

Summary

The use of intracardiac carbon dioxide in negative-contrast roentgenography as a diagnostic procedure in pericardial disease has been outlined. Its rationale, safety, indications, contraindications, precautions, and interpretative clues have been discussed. It is a useful, safe, simple, and rapid procedure when properly employed.

REFERENCES

1. Oppenheimer, M. J., Durant, T. M., Stauffer, H. M., Stewart, G. H., Lynch, T. R., and Barrera, F.: In-vivo visualization of intracardiac structures with gaseous carbon dioxide; cardiovascular-respiratory effects and associated changes in blood chemistry, Am. J. Physiol. **186**:325, 1956.
2. Stauffer, H. M., Durant, T. M., and Oppenheimer, M. J.: Gas embolism; roentgenologic considerations, including the experimental use of carbon dioxide as an intracardiac contrast material, Radiology **66**:686, 1956.
3. Durant, T. M., Stauffer, H. M., Oppenheimer, M. J., and Paul, R. E.: The safety of intravascular carbon dioxide and its use for roentgenologic visualization of intracardiac structures, Ann. Int. Med. **44**:191, 1957.
4. Paul, R. E., Durant, T. M., Oppenheimer, M. J., and Stauffer, H. M.: Intravenous carbon dioxide for intracardiac gas contrast in the roentgen diagnosis of pericardial effusion and thickening, Am. J. Roentgenol. **78**:224, 1957.
5. Scatliff, J. H., Kummer, A. J., and Janzen, A. H.: The diagnosis of pericardial effusion with intracardiac carbon dioxide, Radiology **73**:871, 1959.

The role of exercise tests in the diagnosis of coronary artery insufficiency

Pulmonary and cardiac response to a treadmill work capacity test applicable to patients convalescing from acute myocardial infarction

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This study, using a treadmill walking test, was conducted to determine the per cent of recovery, and, hence, the reproducibility of an exercise period of 10 minutes, repeated after 20 minutes of rest, in healthy but poorly conditioned volunteer physician subjects. Because of the lack of information on cardiopulmonary parameters in the early recovery period after myocardial infarction, this treadmill test was applied to a few patients in an attempt to ascertain whether testing these patients is feasible. The work load was kept constant by individualizing the treadmill belt speed for subjects of different weight. The electrocardiographic response (CR leads) was continuously monitored on the oscilloscope. This test was used to observe the pulmonary ventilation, heart rate, oxygen uptake, and the oxygen extracted from the inspired air during the exercise at a specific work load.

Potgieter[1] has summarized an earlier study of subjects undergoing a treadmill exercise test in our laboratory. He reported the abnormalities of rhythm and S-T-segment displacement that were observed when the electrocardiographic response to exercise was monitored continuously on an oscilloscope during treadmill walking. Since that time, further studies have been made in an attempt to clarify the limitations of this type of exercise test and the significance of the associated S-T-segment changes. These studies are a preliminary approach to a method of selecting patients who might be candidates for endarterectomy.

A change in the electrocardiogram with

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exercise in patients with angina pectoris was reported in 1931, by Wood and Wolferth.[2] They raised the question whether the alterations in the electrocardiograms associated with the attacks of angina pectoris were caused by the exercise, or by temporary myocardial ischemia or the changes in blood pressure and pulse rate which accompanied the attack in patients with coronary artery insufficiency. Although many studies have been made in the interim, much remains to be elucidated about the genesis of these electrocardiographic changes. Continuous monitoring of QRS-T complexes and observance of the changes from the resting observation during exercise gives no direct information on reductions either in coronary blood flow or myocardial oxygen tension, or increases in cardiac oxygen metabolism.

We sought a test procedure which would allow us to make observations during a specific work load for each subject. Such a test, which if repeated either after a short rest period or on a later date, should keep the energy expenditure constant during the treadmill exercise. Having such a test procedure, it was hoped that a method of measuring coronary blood flow other than by the nitrous-oxide method might be developed which could be applied to the patient during rest and repeated while the patient was in a "steady state" during exercise at the predetermined load. Such a method of measuring coronary blood flow during exercise which has advantages over the nitrous-oxide desaturation technique has not yet become available.[3-5]

The present report attempts to show the reproducibility of the test when used in 8 healthy subjects with a double exercise period of 10 minutes. Because there is a "paucity of comprehensive studies of the hemodynamics after acute myocardial infarction,"[6] we also present an assessment of several cardiopulmonary parameters during exercise tests in 3 patients, conducted 6 weeks to 6 months after an episode of acute myocardial infarction.

Methods

The exercise load of Dr. Bruce's treadmill test[7] (10 per cent grade at 1.73 miles per hour for 10 minutes) was found to be tolerated by patients who were able to walk 1.5 to 2.0 miles daily in the hospital corridors, as measured by pedometers, while convalescing from the acute episode and before their discharge from the hospital.

Essentially, the technique of the test was the same as that described by Bruce.[7,8] Potgieter was able to work out a method of eliminating alternating-current interference so that it was possible to obtain acceptable electrocardiographic tracings during exercise as well as a continuously depicted QRS-T complex on the Viso-Scope.* The physician responsible for the safety of the subject monitored the Viso-Scope throughout the experiment. The reports of Yu[9] and Longmire[10] indicate that this approach to evaluation of the electrocardiogram of the exercising patient was feasible in their laboratories.

The protocol of the test is shown in Fig. 1. The healthy subjects, all volunteer males between the ages of 33 and 60 years, were tested at a work load of 370 kilogram-meters per minute for 10 minutes. After a 20-minute rest period, the subjects underwent another 10 minutes of exercise at a work load of 370 kilogram-meters per minute. Individualization of the work load was made possible by using the nomogram (Fig. 2) designed by Potgieter for our treadmill† when set at a 10-degree elevation. The speed of the treadmill belt, needed to give the chosen work load, was selected according to the weight of the subject, and could be monitored by use of the tachometer on the treadmill. The belt speed could be adjusted over a range of 1.5 to 4.0 miles per hour.

The oxygen consumption was obtained by collecting the expired air in a Tissot spirometer and analyzing this sample for the oxygen content by the Scholander method.[11] The remainder of the parameters were recorded as reported by Bruce,[7,8] with electrocardiographic recording as described by Yu.[9]

Results

The data obtained in the 8 subjects are shown in Fig. 3. These observations indicate that recovery to pre-exercise values in this group of 8 healthy male subjects tended to

*Model No. 169, made by Sanborn Company, Waltham, Mass.
†Manufactured by W. E. Quinton Instrument Co., Seattle, Wash., and designated as Model No. 18-49.

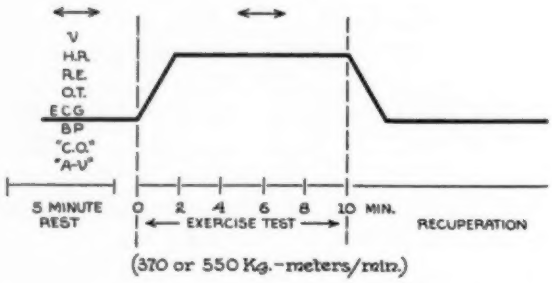

Fig. *1*. Abbreviations on the left-hand side of the figure: *V*, Pulmonary ventilation, liters per square meter per minute; *H. R.*, heart rate; *R. E.*, respiratory efficiency (oxygen extracted from inspired air), volume per cent[7]; *O. T.*, gross oxygen consumption, liters per minute; *ECG*, electrocardiogram; *BP*, blood pressure, millimeters of mercury; "*C. O.*", calculated cardiac output utilizing pulse pressure and heart rate, liters per minute; "*A-V*", systemic arteriovenous oxygen difference based on Fick equation, cubic centimeters per 100 cubic centimeters. The electrocardiogram was monitored throughout the exercise period. The other parameters were measured during the fifth and the sixth minutes of exercise.

be completed within 15 to 20 minutes, two tests having been made on the same occasion. The work load was kept at 370 Kg.M. by use of the nomogram mentioned above when exercise work was performed by these subjects. Tests done on two different occasions on the same individual at the same work load showed acceptable reproducibility.

The healthy "resting" male was found while standing alert to utilize 4.0 ml. of oxygen per kilogram of body weight per minute. Net mechanical efficiency was about 16 per cent, as had been reported by Dill and co-workers.[12] At this level of efficiency the energy expenditure approximates 100 kilogram-meters per minute. This represents the individual's "ready for action" energy expenditure level. The work load used increased the total oxygen consumption 3 to 7 times above that of the "ready for action" level.

Fig. 4 compares the average responses for 24 tests on 7 normal subjects with the average responses of 6 tests made on 3 postmyocardial patients and with 6 tests on 3 patients with primary hypertension taking depressor drugs. These tests were carried on at varying work loads. The subjects with primary hypertension, being healthy, were better able to exercise for 10 minutes at a higher work level, approximating that of the normal subjects, than were the postmyocardial infarction patients.

The resting parameters are at about the same level except for: (1) narrowed pulse pressure of the postmyocardial infarction group, and (2) the higher but essentially top normal systolic and diastolic pressure levels of the hypertensive subjects before exercise. In the small series studied the outstanding changes are the increase in pulse pressure as well as heart rate at the higher work load in the hypertensive subjects. The postinfarction patients' average increase in heart rate is greater than that of the normal subjects but less than that of the hypertensive patients.

Comments

These observations confirm the reports of Bruce, Welch and co-workers[8,13] that the treadmill test is a stress that even postmyocardial infarction patients can tolerate without too much difficulty. With the increased work load used in these exercise tests the postinfarction patients showed an

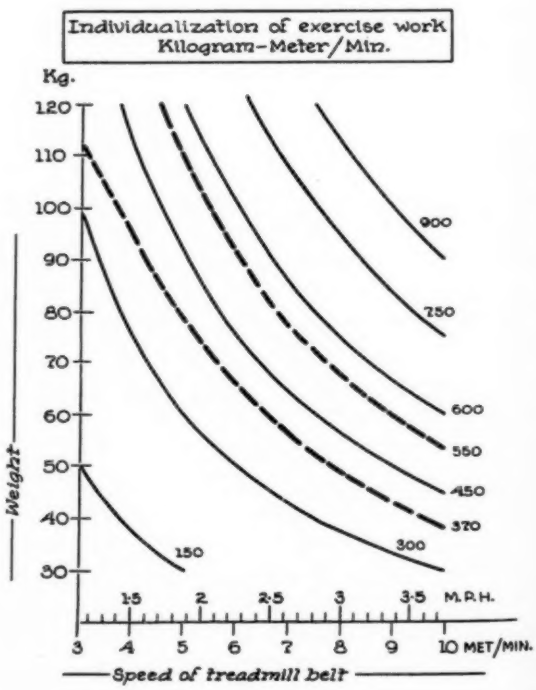

Fig. *2*. Individualization of exercise work in kilogram-meters per minute. This nomogram can be utilized to obtain the belt speed for the treadmill by relating the individual's weight and work load. For a 70-kilogram man to work at 550 Kg.M./min. would require a belt speed setting of 2.9 miles per hour.

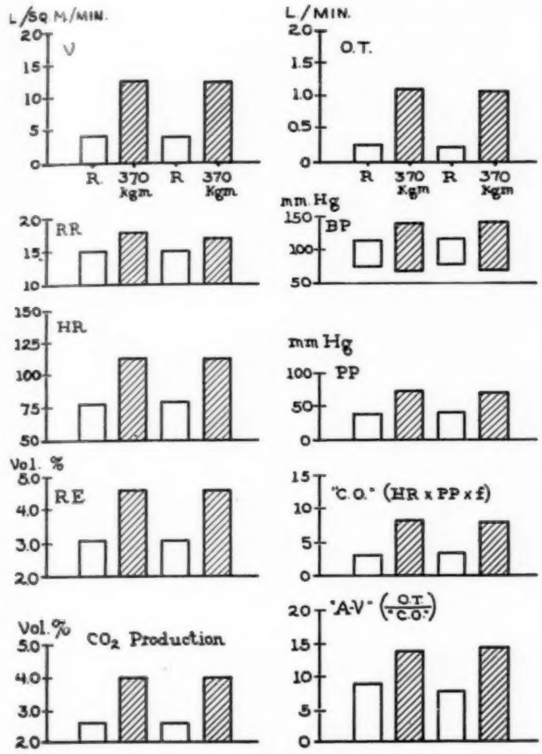

Fig. *3.* Average responses of 8 normal subjects tested during 2 periods of treadmill exercise at 370 Kg.M. work loads with a rest period between. Ventilation (*V*), liters per square meter per minute (*L./Sq.M./min.*); respiration rate (*RR*); heart rate (*HR*); respiratory efficiency (*RE*); carbon-dioxide (CO_2) production; gross oxygen consumption (*O.T.*), liters per minute (*L./min.*); blood pressure (*BP*), with top of bar representing systolic pressure and bottom of bar, diastolic pressure; pulse pressure (*PP*), millimeters of mercury; "cardiac output" ("*C.O.*"), as the product of heart rate, pulse pressure and a factor (*f*), liters per minute; arteriovenous systemic oxygen difference ("*A-V*") as the quotient of total oxygen and "cardiac output" $\left(\frac{\text{O.T.}}{\text{"C.O."}}\right)$, cubic centimeters per 100 cubic centimeters.

augmentation of heart rate. Turell and Hellerstein[6] suggested that if the "pulse rate during effort exceeds 135-140 beats per minute" during a double two-step test of a postinfarction patient, an abnormal response is indicated. All of our postinfarction patients tested at a work load over 200 Kg.M./min., usually between 370 and 450 Kg.M./min., showed a heart rate during exercise of 136 or more beats per minute.

Ford and Hellerstein[14] noted that in patients with arteriosclerotic heart disease the amount of oxygen extracted from the inspired air (R.E.) is reduced. We also observed that, on the average, less oxygen was extracted from the inspired air in the postmyocardial infarction patients than in the other two groups tested.

If an estimate of, or a first approximation to, cardiac output ("C.O.") can be derived from the product of pulse pressure (P.P.) and heart rate (H.R.), the trend for this small sample of hypertensive males is to have a higher product, or resultant, than either the normal subject or the postinfarction patients during the treadmill walk, as shown at the top of Fig. 5. If the ratio of $\frac{\text{Total } O_2}{\text{"C.O."}}$ (from the Fick equation for oxygen and cardiac output) represents systemic A-V difference ("A-V"), then the pre-exercise level in the postinfarction

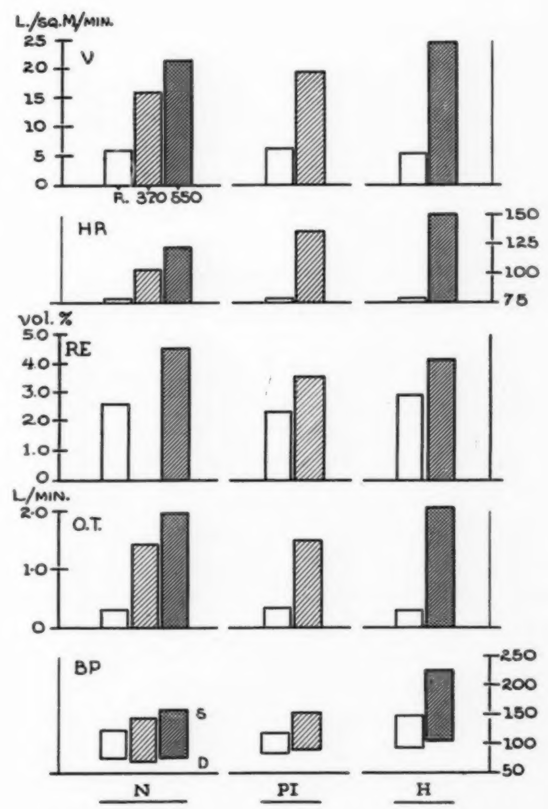

Fig. *4.* The effects of treadmill exercise on pulmonary ventilation (*V*), heart rate (*HR*), respiratory efficiency (*RE*), gross oxygen consumption (*O.T.*), and blood pressure (*BP*), in normal subjects (*N*), postmyocardial infarction (*PI*), and hypertensive patients (*H*). The unlined bars represent resting values; the wide-lined bars, 370-Kg.M. work load values; and the narrow-lined bars, 550-Kg.M. work load values.

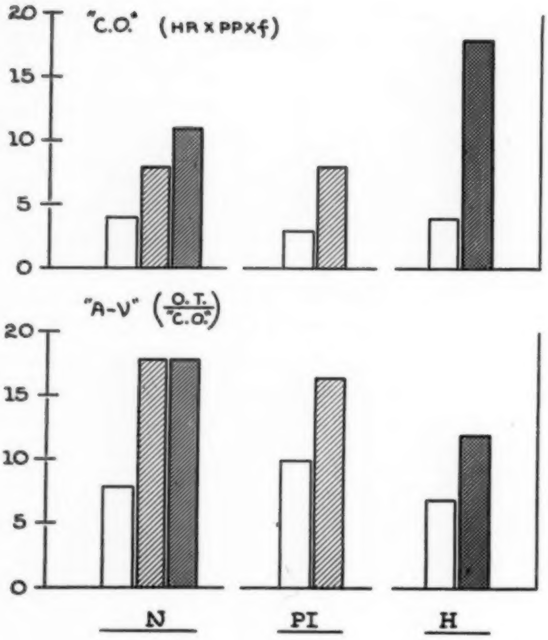

Fig. 5. The effects of treadmill exercise on derived cardiac output ("*C.O.*") and derived systemic arteriovenous oxygen difference ("*A-V*"), in postinfarction patients (*PI*), hypertensive patients (*H*), and normal subjects (*N*). The unlined bars represent resting values; the wide-lined bars, 370-Kg.M. work load values; and the narrow lined bars, 550-Kg.M. work load values.

patients, as shown in the lower part of Fig. 5, suggests that this "resting" A-V difference is essentially the same as that in the "normal" group and increases with exercise about as much as that in the normal group tested.

Between 300 and 600 kilogram-meters, all subjects on retesting showed a linear response of pulmonary ventilation, total oxygen consumption, and heart rate. When the work performed by the three groups of subjects is considered at a gross oxygen consumption of 1.5 liters, the results in Fig. 6 suggest: (a) postinfarction patients had a faster heart rate and performed less work; (b) the amount of oxygen which they extracted (R.E.) from the expired air was less; (c) they were unable to increase pulse pressure; and (d) despite their increased heart rate, their derived cardiac output, "C.O.," increased about twofold, as in normal subjects. The effect of the increased work load (at the same total gross oxygen uptake) in the postinfarction patients was to increase the systemic A-V oxygen difference, "A-V." This is to be expected, since other studies have shown that certain organs extract more oxygen in order to meet the oxygen demands of the more active tissues, such as the heart and skeletal muscles, by encroaching upon the systemic venous oxygen reserve.[5,14-16]

From these experimental data, the only approach is an indirect one as to what might be happening with regard to the extraction of oxygen in the heart muscle.[5,16] Severe changes in mean cardiac oxygen tension affect the myocardial electrical activity,[17] and one would expect this to be reflected eventually in the contraction-to-contraction depiction of the QRS-T complex on the Viso-Scope.

Potgieter observed that the S-T-segment changes do become apparent even at low

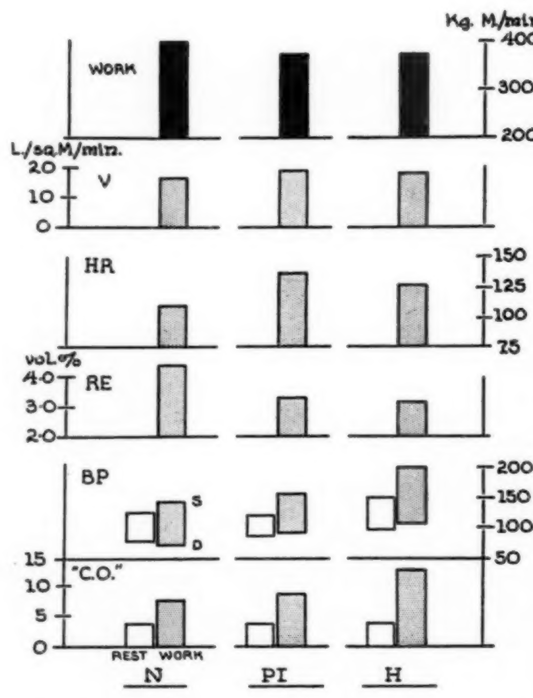

Fig. 6. Bar graph indicating, at the top, the work load in kilogram-meters per minute at a total oxygen consumption of 1.5 liters per minute for each of the three groups tested: *N*, normal subjects; *PI*, post-myocardial infarction patients; and *H*, hypertensive patients. Below the work loads are: *V*, pulmonary ventilation, in liters per square meter per minute; *HR*, heart rate, beats per minute; *RE*, respiratory efficiency (oxygen extracted from inspired air), volume per cent; *BP*, blood pressure, millimeters of mercury, with *S* as the systolic reading and *D*, the diastolic value, with the unlined bars for the values at rest, and the stippled bars for the readings observed at work. "*C.O.*" is the derived cardiac output in liters per minute obtained from the product of pulse pressure, heart rate, and a factor. (See text.)

work loads (200 Kg.M./min.) before the postinfarction patients complain of substernal distress or bothersome breathing effort. Because this QRS-T change is considered to be an unfavorable symbol of "coronary blood flow inadequacy" during exercise, tests on such patients were immediately terminated.

In one of the postinfarction patients, after about 5 minutes of exercise at a lower work level (175-200 Kg.M./min.) and at a time when he had no substernal distress, a negative displacement of about 0.5 millivolts was recorded, and the test was immediately terminated. No untoward reaction ensued. We have observed difficulties from day to day both in eliminating the alternating-current interference and in minimizing the artefacts of muscle tremor and expansion of the chest cage during exercise. This makes careful monitoring difficult. These difficulties make us wary of the use of this type of exercise test response in the selection of patients for endarterectomy as has been described by Kattus and associates.[10]

From these preliminary observations, we believe that further studies are indicated, as follows.

A. Clinical investigation should assess the validity of recommendations for activity of postmyocardial infarction patients by controlled treadmill work level tests. These tests might produce more rational advice as to the role of walking exercise in recovery from an acute myocardial infarction.

1. Patients recovering from acute myocardial infarction, and with resting electrocardiograms back to normal 6 weeks to 6 months after the episode, might be assessed at work loads approaching 370 Kg.M./min., if they can be taught to accustom themselves to lesser treadmill work.

2. Using the "double work period" exercise test described originally by Foltz and co-workers,[18] and applied here to the healthy subjects, might have advantages in testing the cardiopulmonary reserve and recuperative potential of the postmyocardial infarction patient 6 months or more after the acute episode.

B. Patients with abnormal electrocardiograms persisting 6 weeks to 6 months after myocardial infarction must be even more cautiously studied in order to determine what is the most rational prescription of walking activity.

C. The possible use of cinefluorography with such work tests (in an attempt to correlate any changes during the treadmill exercise in frontal surface area which was found to be normal at rest) might assist in the attempt to predict which convalescing infarction patients with persisting abnormal electrocardiograms are most likely to go into the postinfarction congestive heart failure syndrome if ambulated too vigorously.

Summary and conclusions

1. Preliminary studies on 8 healthy male subjects show that the response of ventilation, oxygen uptake, and heart rate to treadmill exercise varying between 300 and 600 kilogram-meters per minute is linear and reproducible.

2. Patients recovering from an acute myocardial infarction, if able to be ambulatory in the period 6 weeks to 6 months after the episode, have been observed to be able to tolerate an exercise work load of 370 Kg.M./min. up to 10 minutes. Our studies of testing at these work levels in selected patients show that the treadmill walk can be performed without undue apprehension, excessive increases in heart rate, or marked S-T-segment displacement in the period 6 weeks to 6 months after myocardial infarction.

3. Although the beat-to-beat recording of the electrocardiogram is not completely satisfactory during exercise, this seems to be as good an approximation to a measurement of coronary blood flow under these conditions as is presently available. The alternative is the use of the more cumbersome nitrous-oxide method as described initially by Bing, Kety, Eckenhoff, and Goodale.

REFERENCES

1. Potgieter, L., Schmitthenner, J. E., Daugherty, E. A., and Hafkenschiel, J. H.: Preliminary report on the work capacity of patients with hypertension and after myocardial infarction, Tr. & Stud. Coll. Physicians Philadelphia **27**:88, 1959.
2. Wood, F. C., and Wolferth, C. C.: Angina pectoris: the clinical and electrocardiographic phenomena of the attack and their comparison with

the effects of experimental temporary coronary occlusion, A.M.A. Arch. Int. Med. **47**:339, 1931.
3. Forte, I. E., Schmitthenner, J. E., and Neal, H.: Coronary blood flow using radioactive iodine compared with nitrous oxide, Circulation Res. **9**:May-June, 1961.
4. Bing, R. J., Hellems, H. K., and Regan, T. J.: Measurement of coronary blood flow in man, Circulation **22**:1, 1960.
5. Lombardo, T. A., Rose, L., Taeschler, M., Tuluy, S., and Bing, R. J.: The effect of exercise on coronary blood flow, myocardial oxygen consumption and cardiac efficiency in man, Circulation **7**:71, 1953.
6. Turell, D. J., and Hellerstein, H. K.: Evaluation of cardiac function in relation to specific physical activities following recovery from acute myocardial infarction, Prog. Cardiovas. Dis. **1**:237, 1958.
7. Bruce, R. A., Lovejoy, F. W., Yu, P. N. G., and McDowell, M. E.: Observations of cardiorespiratory performance in normal subjects under unusual stress during exercise, A.M.A. Arch. Indust. Hyg. **6**:105, 1952.
8. Bruce, R. A.: Evaluation of functional capacity and exercise tolerance of cardiac patients, Mod. Concepts Cardiovas. Dis. **25**:321, 1956.
9. Yu, P. N. G., Bruce, R. A., Lovejoy, F. W., and McDowell, M. E.: Variations in electrocardiographic responses during exercise, Circulation **3**:368, 1951.
10. Longmire, J. P., Jr., Cannon, J. A., and Kattus, A. A.: The surgical treatment of angina pectoris, A.M.A. Arch. Int. Med. **104**:886, 1959.
11. Scholander, P. F.: Analyzer for accurate estimation of respiratory gases in one half cubic centimeter samples, J. Biol. Chem. **167**:235, 1947.
12. Knehr, C. A., Dill, D. B., and Nevfeld, W.: Training and its effects on men at rest and at work, Am. J. Physiol. **136**:148, 1942.
13. Welch, G. E., Bruce, R. A., Bridges, W. C., Johnson, A. D., Lehmann, J. H., and Nielsen, M.: Comparison of a new step test with a treadmill test for the evaluation of cardiorespiratory working capacity, Am. J. M. Sc. **223**:607, 1952.
14. Ford, A. B., and Hellerstein, H. K.: Energy cost of the Master two-step test, J.A.M.A. **164**:1868, 1957.
15. Donald, K. W.: Exercise studies in heart disease, Mod. Concepts Cardiovas. Dis. **28**:529, 1959.
16. Gorlin, R., Messer, J. V., Levine, H. J., Neill, W. A., and Wagman, R. J.: Coronary circulation in health and disease, Med. Clin. North America **44**:1181, 1960.
17. Säyen, J. J., Katcher, A. H., Sheldon, W. F., and Gilbert, C. M., Jr.: The effect of levarterenol on polarographic myocardial oxygen, the epicardial electrocardiogram and contraction in nonischemic dog hearts and experimental acute regional ischemia, Circulation Res. **8**:109, 1960.
18. Foltz, E., Ivy, A. C., and Barborka, C.J.: The use of double work periods in the study of fatigue and the influence of caffeine on recovery, Am. J. Physiol. **136**:79, 1942.

Mitral valvotomy in children

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Mitral valvotomy is a well-established and common operation. It is usually performed in adults, and reports of the operation in the younger age groups are scanty.[1-4] This may be explained by the fact that mitral stenosis is considered to be uncommon in children, and by the reluctance to operate on patients who might suffer from future attacks of rheumatic fever with possible restenosis of the mitral valve.

This report deals with 13 patients who were between 9 and 16 years of age at the time of operation.

Case reports

Case 1. N. Y., a 10-year-old girl, born in Jerusalem, had suffered from cough and attacks of breathlessness since the age of 9 years. Six weeks before hospitalization there was rapid progression of the dyspnea, hemoptysis occurred, and she was bedridden. There was no history of rheumatic fever. On admission there was cyanosis of the lips and fingers, severe dyspnea at rest, and congestion of the neck veins. The apex beat was palpable in the sixth intercostal space in the anterior axillary line. There was a right ventricular uplift, and at the apex a diastolic thrill and a rumbling diastolic murmur were detected. The mitral first and the pulmonic second sounds were accentuated. The edge of the liver was palpable 2 cm. below the costal margin. The pulse rate was 100 per minute, and the blood pressure was 105/75 mm. Hg. A chest x-ray film showed enlargement of the left atrium, the right ventricle, and the pulmonary arteries, with congestion of the lungs. The ECG showed notched and peaked P waves and right ventricular strain. The erythrocyte sedimentation rate was 16/44 mm.

After the heart failure had been controlled with digitalis and diuretics, mitral valvotomy was performed.* The lungs were found to be edematous, and a mitral orifice of 8 mm. was palpated. The fibrotic commissures were split with difficulty, resulting in an opening of 20 mm. Rheumatic activity was not detected in the biopsy of the atrial appendage. The postoperative course was smooth.

Five years after operation she is symptom-free, and has no restriction of her everyday activities. She is not receiving drug therapy.

Case 2. M. M., a 15-year-old boy, born in Morocco, arrived in Israel when he was 9 years old. The following year, on routine examination, a heart murmur was detected, but no history of rheumatic fever was elicited. When he was 12 years old, he suffered from pains in the joints and subfebrile pyrexia, and had an elevated erythrocyte sedimentation rate. Even after this attack he remained symptom-free, but at the age of 15 he was hospitalized for evaluation of the cardiac condition. Examination revealed a normally developed boy with slight cyanosis of the lips. A right ventricular uplift and a presystolic apical thrill were palpated. The first mitral and second pulmonic sounds were accentuated. A diastolic crescendo murmur and a short systolic murmur (Grade 1) were heard over the apex. The pulse was 78 and regular; the blood pressure was 100/70 mm. Hg. There were no signs of peripheral venous congestion. Routine laboratory tests gave findings within normal limits. Chest x-ray examination demonstrated enlargement of the

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*All the valvotomies were performed by Dr. Milwidsky.

Table I. *Preoperative findings in 13 patients*

Case number	*Sex*	*Age at time of operation (yr.)*	*History of rheumatic activity*	*Symptoms leading to operation*		*Grade of incapacitation*	*Presence of apical systolic murmur (grade)*	*X-ray findings*	*ECG*
				Palpitations, dyspnea	*Hemoptysis*				
1.	F	10	−	++	+	++++	−	LA+, RV+, PA+, pulmonary congestion	P+, RVS
2.	M	15	+	−	−	−	1	LA+, RV+, PA+, pulmonary congestion	P+
3.	F	16	Chorea	+++	−	+++	−	LA+, RV++, PA+	P+
4.	F	12	++	++	−	++++	−	LA+, LV+, RV+, PA+	P+, RVS
5.	F	13	++	+	−	+++	−	LA++, pulmonary congestion	RVS
6.	M	9	+	++	−	++++	3	RV+	P+, RVS
7.	M	15	−	++	+++	++++	−	LA+, RV+, PA+, pulmonary congestion	P+, RVS
8.	F	13	+?	+++	+	++++	−	LA++, RV+, PA+	P+, RVS
9.	M	15	−	+	+++	++	−	LA++, RV++, hemosiderosis	P+, RVS
10.	F	10	+	+	−	+	−	LA+, RV+, PA+	RVS
11.	M	14	−	−	−	−	3	LA++, LV+, RV+, PA+	LVS?
12.	F	14	+	+	−	++	2	LA+++, RV+, PA+, LV+	RVS
13.	F	16	++	++	−	++++	2	LA+, RV+, PA+	P+

P+: Notched, peaked, and/or enlarged P waves in standard leads. RVS: Right ventricular strain.

left atrium, right ventricle, and pulmonary arteries, and congestion of the lung fields. The ECG revealed a mitral P. Direct puncture of the left atrium demonstrated a mean pressure of 26 mm. Hg. At operation, a mitral opening of 8 mm. was found. The cusps were fibrotic, particularly in the region of the posterior commissure. The commissures were split and a 20-mm. opening was realized. Histology of the left atrial appendage showed active and healed rheumatic activity.

Five years after operation he is completely symptom-free.

Case 3. R. L., a 16-year-old girl, born in Jerusalem, suffered from chorea at the age of 9 years, but was symptom-free until 3 months before hospitalization, when she began to suffer from severe dyspnea and palpitations on effort, and orthopnea. Clinical examination revealed a slightly cyanotic girl. The apex beat was palpable in the sixth intercostal space, and a diastolic thrill and murmur were found at the apex. The mitral first and the pulmonic second sounds were accentuated. The edge of the liver was palpable 4 cm. below the costal margin. The pulse was 80 and regular; the blood pressure was 95/60 mm. Hg. Chest x-ray examination showed enlargement of the left atrium, right ventricle, and pulmonary artery. The ECG showed notched P waves.

After the patient had been treated with digitalis and antibiotics, mitral valvotomy was performed. The mitral orifice was 10 mm. in diameter, with thickened leaflets and fibrotic commissures. Only the anterior commissure was split, resulting in an opening of 25 mm. without production of regurgitation. Histology of the atrial appendage showed no rheumatic activity. The postoperative course was uneventful. Her exercise tolerance has definitely improved, and 4 years after operation she is working an 8-hour day as a seamstress. During the follow-up period, bilateral bronchiectasis has been detected, which has necessitated continuous prophylactic antibiotic therapy.

Case 4. E. Z., a 12-year-old girl, born in Morocco, had been hospitalized several times during the 5 years prior to the hospitalization now reported, because of recurrent attacks of rheumatic fever. During the last year she had been unable to attend school because of palpitations and dyspnea on effort. Physical examination showed an ill-nourished, cyanosed girl, slightly dyspneic at rest. A tapping apex beat was located in the sixth intercostal space in the mid-clavicular line. A right ventricular uplift and an apical diastolic thrill were felt. The first mitral and the second pulmonic sounds were accentuated, and a rumbling diastolic murmur was heard over the apex. The edge of the liver was palpable 2 cm. below the costal margin. The pulse was 82 and regular; the blood pressure was 90/70 mm. Hg. Chest x-ray examination demonstrated enlargement of the left atrium, both ventricles, and the pulmonary artery; the lungs were congested. The ECG showed notched and peaked P waves and right ventricular

strain. The erythrocyte sedimentation rate was 15/29. Antistreptolysin-O titer was 40 units, and C-reactive protein was negative.

After preparation with digitalis, diuretics, and antibiotics, mitral valvotomy was performed and a 5-mm. orifice was split to 20 mm. Left atrial biopsy revealed active rheumatic myocarditis. The postoperative course was uneventful, and 4½ years after operation she is completely symptom-free and leading a normal active life.

Case 5. S. E., a 13-year-old girl, born in Iraq, had been hospitalized 4 times since the age of 8 years because of recurrent attacks of rheumatic fever. Since the age of 12 she had suffered from progressive shortness of breath on effort, and this, together with signs of smouldering rheumatic activity, was the reason for this fifth admission to hospital. Examination revealed a well-developed girl with venous pulsation in the neck. The apex beat was palpable 2 cm. outside the mid-clavicular line in the fifth intercostal space. A diastolic apical thrill was felt. Auscultation revealed accentuated first mitral and second pulmonic sounds, and an apical diastolic murmur. There were no signs of peripheral venous congestion. The pulse rate was 80 per minute, and the blood pressure was 90/45 mm. Hg. Routine laboratory tests gave findings within normal limits. A chest x-ray film indicated enlargement of the heart, mainly of the left atrium, and engorgement of the pulmonary vasculature. The ECG showed right ventricular strain. Catheterization of the right heart revealed markedly elevated pressures. After she had been treated with steroids, digitalis, and diuretics, mitral valvotomy was

Table II. *Hemodynamic data in 7 patients preoperatively*

Case number	*Right atrial pressure—Mean (mm. Hg)*	*Right ventricular pressure (mm. Hg)*			*Pulmonary arterial pressure (mm. Hg)*			*Wedge pressure—Mean (mm. Hg)*	*Left atrial pressure—Mean. (mm. Hg)*
		Systolic	*Diastolic*	*Mean*	*Systolic*	*Diastolic*	*Mean*		
2.	—	—	—	—	—	—	—	—	26
5.	3	70	2	32	75	35	50	20	—
6.	—	—	—	—	—	—	—	—	31
7.	7	50	5	20	46	26	30	24	—
9.	5	84	4	47	87	38	57	25	—
11.	—	—	—	—	—	—	—	—	33
13.	9	42	8	20	50	25	38	20	—

Table III. *Operative findings and postoperative course in 13 patients*

Case number	*Size of opening and condition of valve*	*Left atrial biopsy findings of rheumatic activity*	*Postcommissurotomy syndrome*	*Duration of follow-up period (yr.)*	*Operative results*	*Remarks*
1.	8 mm., fibrotic	−	−	5	Very good	—
2.	8 mm., fibrotic	+	−	5	Remains symptom-free	—
3.	10 mm., fibrotic	−	−	4½	Very good	Bronchiectasis
4.	5 mm., fibrotic	+	−	4½	Very good	—
5.	10 mm., elastic	+	−	4	Very good	—
6.	15 mm., regurgitation+	+	−	?	?	Lost to follow-up
7.	5 mm., calcified	−	−	2½	Good	Fibrillating
8.	5 mm., calcified	−	−	2	Good	—
9.	12 mm., calcified, regurgitation+	+	−	2	Improved	Recatheterized
10.	10 mm., severely deformed, fibrotic	+	−	2	Good	—
11.	20 mm., regurgitation+++	+	+	2	Unchanged	—
12.	15 mm., fibrotic, severely deformed, regurgitation++	−	+	1	Unimproved	Fibrillating
13.	12 mm., fibrotic, regurgitation+	−	−	1	Good	—

performed. An elastic valve was palpated, with a 10-mm. opening; this was split to 25 mm. The biopsy of the left atrial appendage showed rheumatic activity. The postoperative course was smooth.

Four years after operation she is symptom-free. She has had no further attacks of rheumatic fever.

Case 6. L. B., a 9-year-old boy, on his arrival in Israel from Russia was immediately admitted to hospital because of congestive cardiac failure. When he was 7 years old, he had had active rheumatic fever, and was told that he had a heart lesion. On admission he was found to be dyspneic at rest, with engorgement of the neck veins. A heaving apex beat was located in the fifth intercostal space 2 cm. outside the mid-clavicular line. A right ventricular uplift was palpable. The mitral first and pulmonic second sounds were accentuated. At the apex a Grade 3 blowing systolic murmur, transmitted to the axilla, and a late diastolic rumble were heard. A tender edge of the liver was palpable 9 cm. below the right costal margin. Chest x-ray examination revealed enlargement of the heart in all directions, more pronounced to the right. The ECG showed notched and peaked P waves and right ventricular strain. Left atrial puncture showed a mean pressure of 31 mm. Hg.

After prolonged treatment of the boy with digitalis and diuretics the cardiac failure improved, and the operation was performed. Digital exploration of the mitral valve revealed an orifice 15 mm. in diameter, with marked regurgitation. After complete anterior commissurotomy and partial posterior commissurotomy, an opening of 25 to 30 cm. was achieved. The regurgitation was unaltered. Histology of the left atrial appendage showed rheumatic activity.

Follow-up 2 months later showed improvement, since when he has been lost to follow-up.

Case 7. G. Z., a 15-year-old boy, born in Jerusalem, had suffered from recurrent epistaxis for many years. A heart murmur was detected when he was 11 years old, and since the age of 14 he had suffered from palpitations and dyspnea on effort. Two months before hospitalization he coughed blood, and therafter had fever. Three weeks later he suffered a recurrence of these symptoms, and 8 weeks later he was admitted to hospital after a hemoptysis of one pint of blood. Clinical examination revealed a tall, thin, pale boy, well developed for his age. There was marked engorgement of the neck veins. A slightly heaving apex beat was palpable in the fifth left intercostal space in the mid-clavicular line. A right ventricular uplift and an apical presystolic thrill were palpated. The mitral first and pulmonary second sounds were accentuated; an opening snap and a rumbling diastolic murmur were heard at the apex. The pulse was 100 and regular; the blood pressure was 90/70 mm. Hg. Crepitations were heard over both lung bases. The edge of the liver was palpable 4 cm. below the costal margin, and the tip of the spleen was palpable. There was no peripheral edema. Chest x-ray examination indicated enlargement of the right heart, left atrium, and pulmonary arteries, and pulmonary congestion. The ECG showed enlarged, peaked P waves and right ventricular strain. Catheterization revealed moderately elevated right heart and pulmonary pressures. After he had been treated with digitalis, diuretics, and antibiotics, mitral commissurotomy was performed. At operation the lungs were found to be edematous, and the pulmonary artery was huge. The opening was 5 mm., and was split by finger fracture to 25-30 mm. Because he had difficulty in breathing during the immediate postoperative period, a tracheotomy was performed. Subsequently, his recovery was uneventful. Histology of the left atrial appendage showed no evidence of rheumatic fever.

Twenty months after operation, when he was practically symptom-free, a keloid of his tracheotomy scar was excised under local anesthesia. During this procedure, atrial fibrillation occurred which has resisted conversion. He is at present employed as a laboratory assistant and is working an 8-hour day without difficulty.

Case 8. C. Z., the 12-year-old sister of the previous patient, was hospitalized because of a heart murmur which was discovered on routine physical examination at school. No rheumatic history was elicited, and she denied restriction of her activities. Physical examination revealed an underdeveloped child with congestion of the neck veins and a precordial bulge. A right ventricular uplift was palpable, and there was an apical diastolic thrill and murmur. The first mitral and the second pulmonic sounds were accentuated. There were no signs of peripheral venous congestion. The pulse was 80 and regular; blood pressure was 100/60 mm. Hg. The erythrocyte sedimentation rate was 8/25. Chest x-ray examination showed a very large left atrium and a moderate enlargement of the right ventricle and pulmonary arteries. The ECG showed peaked P waves and right ventricular strain.

Because of the unequivocal clinical diagnosis of mitral stenosis associated with the advanced x-ray and ECG changes, valvotomy was advised. The family, however, did not consent. During the ensuing 18 months, palpitations and dyspnea on effort occurred, and she suffered a febrile episode associated with hemoptysis. Because her symptoms progressed rapidly (she developed dyspnea at rest), and after the successful valvotomy of her brother, the family agreed to operation. Mitral valvotomy was performed despite an erythrocyte sedimentation rate of 111/135 and a sleeping pulse rate of 100. At operation the lungs were edematous and the mitral valve leaflets were fibrotic and calcified, with a 5-mm. orifice. The rigid commissures were difficult to split even with a knife, but a 20-mm. orifice was achieved. Histology of the atrial appendage showed no rheumatic activity.

The postoperative course was smooth, and 2 years after operation she is practically symptom-free for everyday activities, but does tire after forceful effort.

Case 9. Massive hemoptysis, fever, and cough brought A. F., a 15-year-old boy, to hospital a month after his arrival in Israel from Morocco. He gave a 3-year history of palpitations and dyspnea on effort which were aggravated by influenza a month before admission. Physical examination revealed a very pale, thin boy with slight venous engorgement in his neck. A marked right ventricular uplift and an apical presystolic thrill were palpated. The mitral first and pulmonic second sounds were

accentuated. A diastolic rumble was heard over the apex. The edge of the liver was palpable 2 cm. below the costal margin. The pulse was 104, regular, and the blood pressure was 120/80 mm. Hg. Chest x-ray examination showed marked enlargement of the left atrium and the right ventricle and hemosiderosis of the lungs. Kerley lines were visible at both lung bases. The ECG showed tall P waves and right ventricular strain. Right heart catheterization revealed markedly elevated pressures. During a 5-month period of hospitalization he suffered from recurrent attacks of massive pulmonary hemorrhage, which caused fever and marked aggravation of his condition. After his general condition had improved, he was operated on. His lungs were extremely congested, and a mitral opening of 12 mm. was found, together with a mild regurgitant jet. The commissures were rigid and calcified, and the leaflets were fibrotic. Commissurotomy achieved a 25-mm. orifice without increasing the regurgitation. Histology of the left atrial appendage showed rheumatic activity. The postoperative course was complicated by a period of atrial fibrillation, which, however, was converted to sinus rhythm.

Two months after operation he had a slight hemoptysis, but during the following 22 months he remained well and was very much improved subjectively.

Two years after the operation he again had hemoptysis, and he was recatheterized. The pulmonary arterial pressure was now 49/22, mean 33, mm. Hg.

Case 10. H. R., a 10-year-old girl, born in Rumania, was hospitalized because of palpitations and dyspnea on effort, as well as general fatigue. She gave no history of rheumatic fever. Clinical examination showed a well-developed, acyanotic child not dyspneic in bed. There was a slight venous engorgement and pulsation in the neck. The heart was not enlarged. A marked right ventricular uplift and a presystolic apical thrill were palpated. The apical first sound was accentuated, and an opening snap was heard. The pulmonary second sound was accentuated and split. A presystolic rumble was heard over the apex. There were no signs of peripheral venous congestion. All laboratory tests gave findings within normal limits, including C-reactive protein and antistreptolysin-O titer. A chest x-ray film showed enlargement of the left atrium, right ventricle, and pulmonary arteries. The ECG indicated right ventricular strain. At operation the free edges of the mitral valve leaflets were found to be fibrotic, and the anterior commissure was severely deformed. The orifice was 10 mm. in diameter, and was split with difficulty to an opening of 25 mm. Histopathology of the left atrial appendage showed active rheumatic endocarditis.

Two years postoperatively she is very much improved.

Case 11. On routine examination, O. L., a 14-year-old boy, born in Iran, was found to have a heart murmur. He denied any limitation of activity or any other symptoms. No rheumatic history was elicited. Examination revealed a well-developed boy. The apex beat was slightly heaving in character, but was located within the mid-clavicular line. A systolic thrill was palpable at the apex. The mitral first and pulmonic second sounds were accentuated. A harsh systolic murmur with maximum intensity at the apex and a rumbling apical diastolic murmur were heard. The pulse rate was 76 per minute and regular; the blood pressure was 120/75 mm. Hg. Laboratory tests gave findings within normal limits. Chest x-ray examination showed enlargement of both ventricles, a large left atrium, and prominent pulmonary arteries. The ECG suggested left ventricular strain. Left atrial puncture showed a mean pressure of 33 mm. Hg, and the a-c and v waves were of equal height. Operation was decided upon because of the assumption that the stenosis of the mitral valve was the predominant lesion. At operation a mitral valve opening of 20 mm. was found, with a marked regurgitant jet, mainly from the posterior commissure. The anterior commissure was split, giving an opening of 25 mm. without increasing the regurgitation. The left atrial biopsy revealed active rheumatic endocarditis.

Nine months after operation he was readmitted because of symptoms suggesting postcommissurotomy syndrome. He improved without specific treatment. Two years after operation he is symptom-free, as he was preoperatively.

Case 12. S. M., a 14-year-old girl, born in Iraq, had suffered for many years from recurrent tonsillitis. Four years prior to admission she had had one attack of acute rheumatic fever. For 2 years before admission she had had dyspnea and palpitations on moderate effort, and she had suffered from orthopnea. Examination on admission demonstrated a well-developed girl, not dyspneic at rest. The apex beat was diffuse and heaving, and located in the sixth intercostal space, 1 cm. outside the mid-clavicular line. A right ventricular heave and an apical diastolic thrill were palpable. The apical first and pulmonic second sounds were accentuated. A Grade 2 blowing systolic murmur and a rumbling diastolic murmur were heard over the apex, and a loud Grade 2 systolic murmur was heard over the pulmonic area. The edges of the liver and spleen were just palpable. There were no signs of peripheral venous congestion. The pulse was 90 and regular; blood pressure was 115/75 mm. Hg. Routine laboratory tests included erythrocyte sedimentation rate, antistreptolysin-O titer, and C-reactive protein, and the findings were within normal limits. Chest x-ray examination demonstrated a giant left atrium and moderate enlargement of both ventricles and the pulmonary artery. The ECG showed right ventricular strain.

Although the clinical diagnosis of some degree of mitral incompetence was well established, it was thought that relief of the mitral stenosis would improve her condition. At operation the mitral valve was found to be severely fibrotic and deformed. The mitral opening was 15 mm. in diameter, and a marked regurgitant jet was felt. The anterior commissure was completely split, but the short posterior commissure was untouched. An opening of 25 mm. was attained without increasing the regurgitation. Atrial fibrillation occurred immediately after opening the chest and persisted. Biopsy of the left atrial appendage showed no rheumatic activity. The postoperative course was smooth.

Six weeks after operation she was hospitalized because of the clinical picture of postcommissurotomy syndrome, and 6 months later an unsuccessful attempt was made to convert the atrial fibrillation. Her condition remains unimproved.

Case 13. S. Y., a 16-year-old girl, born in Iraq, emigrated to Israel at the age of 8 years. During her early childhood she had had numerous bouts of tonsillitis, usually accompanied by fever. Since the age of 7 years she had experienced dyspnea and palpitations on effort. At the age of 14 she was hospitalized for rheumatic fever. During this admission, right heart catheterization revealed moderately elevated pressures. After this she suffered from intermittent bouts of arthralgia which necessitated hospitalization twice, and for which she received salicylate and corticosteroid therapy. Because her incapacity increased and her arthralgia continued, she was once again admitted to hospital for evaluation for operation. Physical examination revealed a well-developed girl. A presystolic thrill was palpable at the apex. The mitral first and pulmonic second sounds were accentuated. A presystolic crescendo murmur and a blowing systolic murmur (Grade 2) were detected at the apex. The edge of the liver was palpable 2 cm. below the costal margin. The erythrocyte sedimentation rate was 36/72. Antistreptolysin-O titer and C-reactive protein were within normal limits. The ECG revealed notched P waves. X-ray examination demonstrated enlargement of the left atrium, right ventricle, and pulmonary artery. After preparation with corticosteroids she was operated upon. A moderate regurgitant jet was palpated, and the 12-mm. stenosed fibrotic mitral valve was split to 25 mm. without apparent increase of the regurgitation. Biopsy of the atrial appendage showed no signs of active rheumatism.

One year after operation, on limited activity, her condition is satisfactory, and she has had no rheumatic exacerbation.

Discussion

The 13 cases described in the foregoing section constitute 7.5 per cent of the mitral valvotomies performed in our service. This is an unusually high incidence. Angelino and associates,[3] who advocate commissurotomy in children and adolescents in selected cases, report on 11 operations performed in this age group, out of a total of 600 valvotomies. Glover,[5] in a series of 1,500 cases of mitral valvular disease, found valvotomy indicated in less than a dozen instances in patients under the age of 18 years. Bailey and Bolton,[6] in a series of 1,000 commissurotomies, report on only 13 patients under the age of 20 years. They record the youngest patient operated on for rheumatic mitral stenosis—a 4½-year-old girl. The prevalence of mitral stenosis in the young reported here may be explained by the high incidence of rheumatic fever in Israeli children,[7] particularly in Jerusalem.[8] Eight of our children were either born in Jerusalem or lived there from an early age. The records of the pediatric department of this hospital show that the first attack of rheumatic fever occurred below the age of 5 years in 20 per cent of 122 patients hospitalized for this disease, contrary to the generally accepted observation that rheumatic fever is rarely seen below the age of 6 years.[9] This very early appearance of rheumatic fever may account for the relatively early occurrence of valvular damage in our population.

The clinical picture presented by the 13 children was very similar to that seen in adults. Palpitations and difficulties in breathing were the presenting symptoms in nearly all cases. In addition, 5 patients presented with hemoptysis, which was massive in 2 cases (Cases 7 and 9). In these 2 patients the bleeding resembled the "paroxysmal pulmonary hemorrhage" described by Oppenheimer and Schwartz,[10] in 1933, and later called "pulmonary apoplexy" by Wood.[11] A striking feature was the severe, rapidly developing incapacitation suffered by 7 of the children. Despite the absence of confirmatory laboratory tests, their rapid deterioration was suggestive of continuous rheumatic activity; but in only 3 of these patients were Aschoff bodies found in the left atrial appendage. There were 4 other patients who had positive left atrial biopsies, and in these there was neither clinical nor laboratory evidence of rheumatic activity. In 4 patients, right heart catheterization was performed preoperatively, and elevation of the pulmonary arterial pressure was determined. Because of suspected concomitant mitral incompetence, direct left atrial puncture was performed in 3 children, and the mean atrial pressure was found to be between 26 and 33 mm. Hg. Even in the symptom-free patients, marked x-ray and electrocardiographic changes were evident.

When clinical symptoms and/or hemodynamic changes of mitral stenosis are progressive, we believe that the presence of rheumatic activity does not contraindicate mitral valvotomy in selected cases, even in young children. Two patients (Cases 5 and 13) suffered recurrences of clinical rheumatic activity during a period of 5 years,

despite prophylactic penicillin therapy. Both were operated on during a phase of clinically low-grade activity, after preparation with steroids. During a postoperative period of 4 and 1 years, respectively, neither patient has had rheumatic flare-up, and both have been symptom-free. This tends to support the opinion of Bradlow and Crawshaw[2] that mitral stenosis in itself may be a more dangerous condition than rheumatic fever. The severe valvular deformity, fibrosis, and calcification found in these children at operation suggest that the pathophysiologic changes which occur in children are in no way different from those in adults, and may occur after only a few years of illness.

The patients were followed up regularly once in 6 months; a history was obtained, physical and chest x-ray examinations were performed, and an electrocardiogram was recorded. In the 12 patients whom we have been able to follow up, we have no evidence of reactivation, exacerbation, or aggravation of the rheumatic activity. All have been kept on prophylactic penicillin therapy. Two patients (Cases 11 and 12) presented the postcommissurotomy syndrome, a condition not proved to be of rheumatic origin.[12] The incidence of this syndrome was about the same among the children as among the adults operated on in our hospital.[13] No restenosis has occurred during a follow-up period of up to 5 years. The postoperative course of these children was usually smooth, and there was no mortality. It was most gratifying to observe the rapid physical and mental development of most of the children after operation, particularly since some were underdeveloped preoperatively. Two patients with regular rhythm before the operation now have fibrillation, which has resisted all attempts at conversion.

Summary

Report is made of 13 children between the ages of 9 and 16 years who underwent mitral valvotomy. The clinical, hemodynamic, and pathologic findings were the same as those in adults. The operative results were satisfactory; 9 children showed definite clinical improvement. No rheumatic reactivation or restenosis has occurred during a follow-up period of 1 to 5 years.

In our opinion, progressive mitral stenosis should be relieved surgically, whatever the age of the patient.

REFERENCES

1. Lurie, P. R., and Shumacher, H. B.: Mitral commissurotomy in childhood, Pediatrics **13**:454, 1954.
2. Bradlow, B. A., and Crawshaw, G. R.: Mitral valvotomy in the younger age groups, South African M. J. **29**:639, 1955.
3. Angelino, P. F., Levi, V., Brusca, A., and Actis-Dato, A.: Mitral commissurotomy in the younger age group, AM. HEART J. **51**:916, 1956.
4. Gray, I. R.: Mitral valvotomy in the young, Lancet **2**:1263, 1958.
5. Glover, R. P.: Mitral surgery in a young girl, Am. J. Cardiol. **4**:132, 1959.
6. Bailey, C. P., and Bolton, H. E.: Criteria for and results of surgery for mitral stenosis, New York J. Med. **56**:825, 1956.
7. Brand-Aurban, A.: The epidemiology of rheumatic fever in Israel, Harefuah **57**:58, 1959.
8. Eiges, A., Braun, K., Szabo, M. A., Shor, S., and Schwartz, A.: Prevalence of rheumatic heart disease among elementary and secondary school pupils in Jerusalem, Harefuah **58**:254, 1960.
9. Keith, J. D., Rowe, R. D., and Vlad, P.: Heart disease in infancy and childhood, New York, 1958, The Macmillan Co., p. 612.
10. Oppenheimer, B. S., and Schwartz, S. P.: Paroxysmal pulmonary hemorrhages: syndrome in young adults with mitral stenosis, AM. HEART J. **9**:14, 1933.
11. Wood, P.: Appreciation of mitral stenosis: clinical features, Brit. M. J. **1**:1051, 1954.
12. Dresdale, D. T., Ripstein, C. B., Guzman, S. V., and Greene, M. A.: Postcardiotomy syndrome in patients with rheumatic heart disease, Am. J. Med. **21**:57, 1956.
13. Rosenberg, S. Z., Braun, K., and Stern, S.: Postcommissurotomy syndrome, Harefuah **53**:1, 1957.

Experimental and laboratory reports

Acute circulatory effects of arterial bleeding as determined by indicator-dilution curves in normal human subjects

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Blood volume is recognized as an important factor in cardiac regulation. In oligemic shock, cardiac output is clearly reduced.[1] Acute expansion of plasma volume in normal human beings and in patients with mitral stenosis elevates cardiac output and stroke volume.[2] However, previous studies of cardiac output, utilizing the Fick principle and an assumed steady state, have shown conflicting results after venesection in man. After removal of 420 ml. of blood, McMichael and Sharpy-Schafer[3] reported considerable reduction in cardiac output. Warren and colleagues,[4] however, failed to demonstrate significant acute changes in blood flow after depletion of blood volume by 300 to 900 ml. in 12 normal men. Cardiac output, as approximated by the ballistocardiogram, showed little variation after a phlebotomy of 500 ml., but a significant fall was noted when 1 liter of blood was removed.[5] In the anesthetized dog, hemorrhage is accompanied by a transient fall in cardiac output and stroke volume.[6-8]

The distribution of blood volume is probably of significance in the regulation of cardiac output. Sjöstrand[9] has proposed the concept of a depot in the pulmonary circulation which can be mobilized to increase stroke volume and cardiac output in response to systemic demands. The hemodynamic effects of postural changes in human beings may be explained in part by the influence of gravity on the "central blood volume" (CBV).[10]

Since hemodynamic responses to depletion of blood volume in man have not been clearly established, the acute circulatory effects of arterial bleeding in normal subjects were investigated. An indicator-dilution technique was used to measure cardiac output, since this minimized the requirements for a steady state, and also afforded some insight into the distribution of blood volume.

Material and methods

Nineteen male volunteers, who ranged in age between 21 and 33 years, served as subjects. All of them were normal by history, physical, chest x-ray, and electrocardiographic examinations. Studies were performed while the subjects were lying supine and breathing room air. No premedication was given. A No. 6 or 7 cardiac catheter was introduced into the right atrium via a right antecubital vein. A No.

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$$(1) \quad TSR\ (dynes\ sec.\ cm.^{-5}) = \frac{Mean\ Arterial\ Pressure\ (mm.\ Hg) \times 1{,}332 \times 60}{Cardiac\ Output\ (L./min.)}$$

17T Cournand needle was placed in the left brachial artery.

With a calibrated syringe, 15 mg. of Evans blue dye* was rapidly injected into the right atrium via the catheter. Samples of arterial blood were collected in 10-by-75-mm. glass tubes which contained a few granules of dried heparin. These tubes were placed upright in a motor-driven collecting device, adjusted so that each tube sampled arterial blood for 2 seconds. A sample of arterial blood was collected 10 minutes after the injection of the dye for estimation of plasma volume. An electrocardiogram was recorded during each dye curve.

By means of the arterial cannula, 7 or 8 ml. of blood per kilogram of body weight were withdrawn in about 8 minutes. The blood was collected in standard vacuum donor bottles which contained 120 ml. of A-C-D Solution "B" anticoagulant.† A second indicator-dilution curve was obtained immediately after the arteriotomy in the manner described above. The blood was replaced at the termination of the procedure.

Right atrial and brachial arterial pressures were recorded immediately after each dye curve, by means of Statham P23D strain-gauge transducers and a direct-writing Sanborn recorder. The "zero" reference point was taken to be 10 cm. anterior to the spine. Mean pressures were determined planimetrically from their phasic records.

Samples of blood were centrifuged at 2,260 G. for 30 minutes. Optical densities of undiluted plasma in microcuvettes were read twice at 620 millimicrons in a Beckman Model DU spectrophotometer. Indicator-dilution curves were constructed from the plasma concentration of Evans blue dye and plotted on semilogarithmic graph paper. Cardiac output, mean transit time, and CBV were calculated by the Hamilton method as modified by Lilienfield and Kovack.[11] The mean transit time from the right atrium to brachial artery was determined by substracting the transit time of the collecting catheter from the calculated mean transit time of the dye curve. The total systemic resistance was calculated from Equation 1 (*top of page*).

Changes in the variables were statistically analyzed by the student-t test.[12] Correlation coefficients were obtained on all data, by means of an IBM-650 digital computer.

*Warner-Chilcott Laboratories.
†Cutter Laboratories.

Results

The measured and calculated data obtained before and immediately after arterial bleeding of 460 to 900 ml. are presented in Table I and Fig. 1; correlation coefficients are shown in Tables II and III.

1. Changes in volume and distribution. Initially, the average CBV was 1,567 ml., or 26.2 per cent of the average total blood volume. Immediately after bleeding there was a small, but significant (p = .004) reduction in CBV to 1,455 ml. Since the latter volume amounted to 27 per cent of the total blood volume, there was no gross

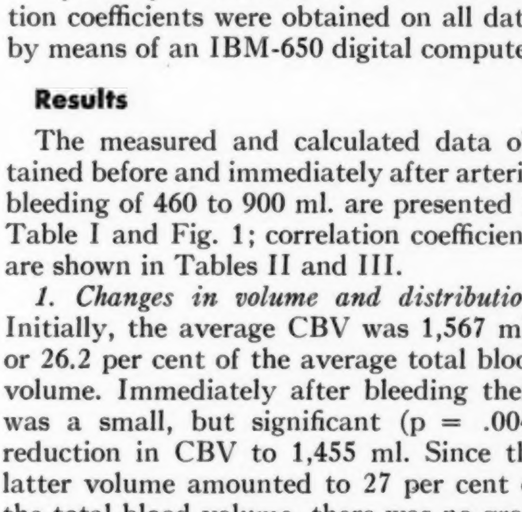

Fig. *1.* Changes after bleeding, expressed as per cent change (*above*) and mm. Hg (*below*). *T.B.V.:* Total blood volume. *C.O.:* Cardiac output. *S.V.:* Stroke volume. *C.B.V.:* Central blood volume. *H.R.:* Heart rate. *M.T.T.:* Mean transit time. *R.A.P.:* Right atrial pressure. *B.A.P.:* Brachial arterial pressure. *T.S.R.:* Total systemic resistance. *Hct.:* Hematocrit.

Table I. *Hemodynamic data before and after arteriotomy*

Subject (*BSA-M.*^{2})	*Total blood volume** (*L.*)	*Cardiac output* (*L./min.*)	*Heart rate* (*beats/min.*)	*Stroke volume* (*ml.*)	*Mean transit time* (*sec.*)	*Central blood volume* (*L.*)	*Arterial hematocrit* (*%*)	*Mean right atrial pressure* (*mm.Hg*)	*Mean brachial arterial pressure* (*mm.Hg*)	*Total systemic resistance* (*dynes sec. cm.*$^{-5}$)
1. W.A.	(c) 5.33	7.71	81	95.2	8.6	1.10	43.5	6.3	93.0	904
(1.81)	(a) 4.41	7.68	74	104.2	10.3	1.32	43.5	3.3	93.0	903
2. S.E.H.	(c) 6.41	6.15	50	122.3	17.0	1.74	41.0	7.1	87.2	1,134
(2.04)	(a) 5.88	5.98	55	108.7	16.5	1.64	39.5	2.4	83.8	1,121
3. W.C.	(c) 5.16	5.66	62	91.3	14.2	1.34	44.5	5.1	86.0	1,215
(1.84)	(a) 4.62	5.18	61	84.9	13.7	1.18	44.5	1.6	85.3	1,317
4. T.S.	(c) 6.11	9.91	75	132.1	10.7	1.77	46.0	2.0	96.0	775
(1.93)	(a) 5.56	8.99	74	121.2	10.9	1.63	44.5	1.0	76.0	676
5. G.A.	(c) 5.81	9.21	72	127.9	11.3	1.73	49.0	1.3	76.0	660
(1.88)	(a) 5.26	5.80	61	95.1	16.0	1.55	48.0	0.5	80.0	1,103
6. S.T.H.	(c) 6.24	6.61	60	111.1	15.9	1.75	46.0	8.1	98.2	1,185
(2.04)	(a) 5.69	6.55	57	114.3	16.8	1.83	45.5	5.7	99.4	1,214
7. N.M.	(c) 6.33	8.26	66	125.7	15.8	2.17	48.0	3.4	86.0	833
(2.12)	(a) 5.77	7.37	64	115.7	16.5	2.03	47.5	1.3	84.8	920
8. P.B.	(c) 4.65	8.05	60	134.2	11.4	1.53	50.5	2.4	106.5	1,058
(1.90)	(a) 4.09	7.14	72	99.4	11.2	1.33	50.5	1.8	102.0	1,143
9. J.C.K.	(c) 7.06	6.05	67	90.7	13.2	1.33	43.2	5.0	86.0	1,137
(1.90)	(a) 6.49	5.55	67	82.7	14.3	1.32	42.0	4.5	90.0	1,297
10. J.T.K.	(c) 7.00	7.45	59	126.3	15.6	1.94	44.0	4.3	84.0	902
(2.04)	(a) 6.41	6.62	51	129.8	17.8	1.97	43.5	3.5	91.4	1,105
11. E.H.T.	(c) 6.30	8.10	76	107.1	12.0	1.62	50.0	3.4	103.2	1,019
(2.06)	(a) 5.71	6.87	77	89.7	12.2	1.40	50.0	0.4	98.0	1,141

*(c): Control. (a): After arteriotomy.

alteration in the distribution of blood between the central and peripheral reservoirs.

2. Changes in flow. Arterial bleeding produced a significant decrease in cardiac output and stroke volume ($p < .001$). The changes in cardiac index were correlated with the change in stroke index ($r = +0.63$), but not with the heart rate, which remained unchanged in most instances. A significant correlation ($r = +0.60$) was noted between the changes in stroke volume and CBV (Fig. 2). Neither the heart rate nor mean transit time changed significantly, yet there was a high correlation between heart rate and mean transit time before bleeding ($r = +0.87$). The largest change in heart rate was in Subject L. R., who experienced transient symptoms of acute circulatory collapse, characterized by bradycardia, pallor, hypotension, and sweating, 6 minutes prior to the second dye curve.

3. Changes in pressure and resistance. Right atrial pressures decreased in all but one subject, from an average of 4.3 to 2.4 mm. Hg. These changes were not correlated with changes in either stroke volume or cardiac output. Only a small fall of 4 mm. Hg. in mean brachial arterial pressure was noted. The total systemic resistance increased 11 per cent ($p = .03$), probably due to lowered cardiac output. The changes in cardiac index and systemic resistance were highly correlated ($r = -0.70$) (Fig. 3).

Discussion

Accompanying the reduction in total blood volume by the experimental procedure of arterial bleeding was a proportionate decrease in "central blood volume" (CBV) and a fall in stroke volume. Since there was no compensatory increase in heart rate under these experimental conditions, cardiac output showed a corresponding decrease. The changes in stroke volume were directly correlated with the changes in CBV ($p < .001$) (Fig. 2); prior to bleeding there was a similar, albeit less significant ($p < .01$), correlation between these parameters. These observations are in accord with those of Johnson[13] on the effects of anesthesia, as well as those of Weissler and associates[10] on the cardiac response to postural changes and to antigravity suits. The inotropic effect of isoproterenol is also associated with an enhancement of CBV.[14] Thus, under several experimental conditions in man the stroke output of the heart has shown a close relationship to the CBV, supporting the concept of a central blood reservoir as a determinant of left ventricular diastolic filling.[9]

In the present study there was no significant correlation between the changes in cardiac output and CBV with removal of blood. Although cardiac output is utilized

Table I. *Hemodynamic data before and after arteriotomy*—Cont'd

Subject (*BSA-M.²*)	*Total blood volume** (*L.*)	*Cardiac output* (*L./min.*)	*Heart rate* (*beats/min.*)	*Stroke volume* (*ml.*)	*Mean transit time* (*sec.*)	*Central blood volume* (*L.*)	*Arterial hematocrit* (*%*)	*Mean right atrial pressure* (*mm.Hg*)	*Mean brachial arterial pressure* (*mm.Hg*)	*Total systemic resistance* (*dynes sec. cm.⁻⁵*)
12. M.P.	(c) 4.31	7.82	67	116.7	9.8	1.28	53.5	5.2	96.4	986
(1.84)	(a) 3.71	6.83	73	94.0	9.3	1.06	49.5	0.7	89.0	1,042
13. W.L.	(c) 5.41	7.34	72	102.4	10.5	1.28	43.0	3.0	84.0	916
(2.06)	(a) 4.81	6.52	80	81.8	11.8	1.28	43.0	2.0	85.0	1,043
14. E.M.T.	(c) 5.91	9.64	71	135.8	10.3	1.65	42.0	—	95.5	793
(2.03)	(a) 5.31	9.82	76	129.2	9.0	1.47	41.0	—	92.6	754
15. P.H.	(c) 5.90	6.17	52	119.8	16.7	1.72	44.5	4.0	92.4	1,198
(2.08)	(a) 5.29	5.33	52	103.5	13.3	1.18	44.5	4.5	81.9	1,229
16. D.F.	(c) 9.14	9.60	76	126.3	10.0	1.60	44.5	4.0	98.8	823
(2.11)	(a) 8.52	7.71	80	95.8	10.2	1.31	43.0	1.4	89.3	926
17. C.H.	(c) 6.16	10.62	82	128.9	7.8	1.38	48.0	4.7	112.8	850
(1.88)	(a) 5.53	8.73	74	117.2	10.0	1.45	46.5	0.9	98.1	899
18. L.R.	(c) 3.74	8.13	78	104.2	10.4	1.41	41.0	2.6	86.0	846
(1.98)	(a) 2.95	5.92	66	89.7	14.2	1.40	39.5	2.3	73.1	988
19. L.C.	(c) 6.24	7.47	69	108.3	11.3	1.41	47.5	5.7	84.0	899
(2.02)	(a) 5.34	5.93	72	82.4	12.8	1.26	47.5	5.2	88.0	1,187
Mean	(c) 5.96	7.89	68	116.1	12.3	1.57	45.8	4.3	92.2	954
± S.D.	1.20	1.38	9.0	14.2	2.7	0.26	3.3	1.7	8.9	157
Mean	(a) 5.36	6.87	68	102.1	13.0	1.46	44.9	2.4	88.5	1,053
± S.D.	1.20	1.24	9.1	15.2	2.7	0.26	3.2	1.6	7.6	169.5
Mean change	−0.60	−1.02	0	−14.0	+0.7	−0.11	−0.9	−1.9	−3.7	+99
p	<0.001	<0.001	0.77	<0.001	0.10	0.004	<0.001	<0.001	0.05	0.03

*(c): Control. (a): After arteriotomy.

Table II. *Correlation coefficients* of control values*

Parameter	*Total blood volume index*	*Cardiac index*	*Heart rate*	*Stroke index*	*Central blood volume index*	*Mean transit time*	*Right atrial pressure*	*Brachial arterial pressure*	*Total systemic resistance*
Total blood volume index		0.07	0.05	0.02	0.19	0.09	0.18	0.06	−0.09
Cardiac index			0.73	0.69	0.06	−0.77	−0.50	−0.42	−0.79
Heart rate				0.01	−0.39	−0.87	−0.34	0.23	−0.67
Stroke index					0.49	−0.22	−0.40	0.37	−0.47
Central blood volume index						0.57	−0.25	−0.13	−0.19
Mean transit time							0.32	−0.35	0.58
Right atrial pressure								0.08	0.60
Brachial arterial pressure									0.12

*Coefficients greater than 0.60 are underlined.

Table III. *Correlation coefficients* of changes after arteriotomy*

Changes in	*Total blood volume index*	*Cardiac index*	*Heart rate*	*Stroke index*	*Central blood volume index*	*Mean transit time*	*Right atrial pressure*	*Brachial arterial pressure*	*Total systemic resistance*
Total blood volume index		0.42	0.13	0.34	0.05	−0.28	−0.32	−0.07	−0.40
Cardiax index			−0.06	0.63	0.19	−0.63	−0.26	0.08	−0.70
Heart rate				−0.68	−0.53	−0.30	−0.02	0.26	0.18
Stroke index					0.60	−0.04	−0.18	0.03	−0.43
Central blood volume index						0.58	−0.12	0.14	−0.06
Mean transit time							0.24	0.22	0.63
Right atrial pressure								0.22	0.41
Brachial arterial pressure									0.63

*Coefficients greater than 0.60 are underlined.

in the calculation of CBV, the other parameter which appears in the formula (mean transit time) is an independent variable, and, as discussed by Rapaport and associates,[15] a correlation between cardiac output and CBV is not an inherent mathematical certainty. The data reported here, as well as the above-mentioned studies, indicate that the principal correlation is that between stroke volume and CBV, rather than between cardiac output and CBV. Recent studies in patients with the chronic hypervolemia of polycythemia vera have shown excellent correlation between total volume and resting stroke volume.[16]

Another consequence of the reduced vol-

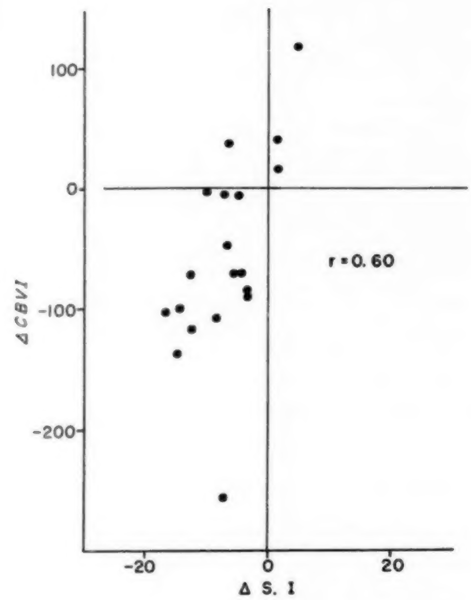

Fig. *2*. Relationship between the *changes* in stroke index and "central blood volume" per square meter.

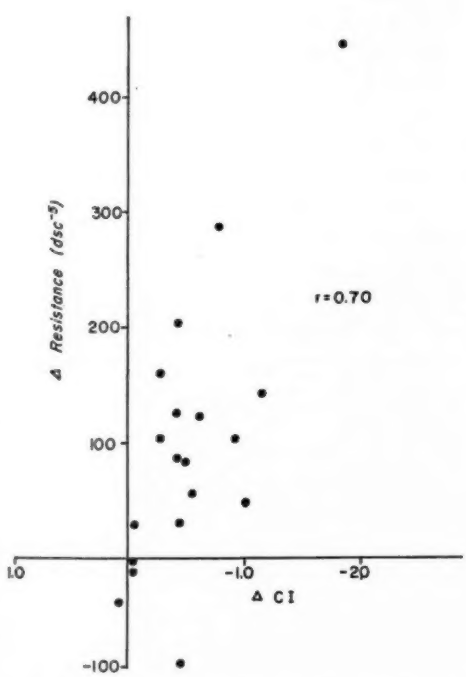

Fig. *3*. Relationship between the *changes* in cardiac index and systemic resistance.

ume of blood was a fall in right atrial pressure. This change, however, was not correlated with the change in blood flow or stroke volume. This is in accord with the observations made by Holt[7] on anesthetized dogs in which the changes in stroke volume were correlated with the changes in left ventricular end-diastolic volume, but not with effective end-diastolic pressure. Since neither end-diastolic nor effective filling pressures were measured in the subjects reported here, it is beyond the scope of this paper to evaluate the significance of measurements of pressure in relation to the Frank-Starling law of the heart. The effect of the removal of blood on stroke volume and CBV, however, is in accord with this principle.

The significant inverse correlation between the changes in cardiac output and systemic resistance is related to a negligible fall in blood pressure; although this is interpreted as representing a compensatory mechanism to maintain systemic pressure and facilitate optimal perfusion, a causal relationship cannot be established from these studies. A primary role of peripheral resistance in regulating cardiac output has been advanced by Hamilton.[17]

Summary

1. Arterial bleeding of 460 to 900 ml. in 19 normal young male adults produced an immediate and significant reduction in cardiac output, stroke volume, and "central blood volume" (CBV). Only minor alterations were noted in heart rate or brachial arterial pressure. Small elevations in mean transit time and total systemic resistance were observed.

2. The "central blood volume" decreased in proportion to the total blood volume, suggesting no significant redistribution of blood volume after arteriotomy.

3. A significant correlation was observed between the changes in stroke volume and "central blood volume," supporting the concept of a central "reservoir" in maintaining stroke volume.

4. The changes in systemic resistance were inversely related to changes in cardiac output.

5. Although a fall in right atrial pressure occurred after arteriotomy, it was not correlated with changes in cardiac output or stroke volume.

REFERENCES

1. Cournand, A., Riley, R. L., Bradley, S. E., Breed, E. S., Noble, R. P., Lauson, H. D., Gregersen, M. I., and Richards, D. W.: Studies of the circulation in clinical shock, Surgery **13**:964, 1943.
2. Schnabel, T. G., Eliasch, H., Thomasson, B.,

and Werkö, L.: The effect of experimentally induced hypervolemia on cardiac function in normal subjects and patients with mitral stenosis, J. Clin. Invest. **38**:117, 1959.
3. McMichael, J., and Sharpy-Schafer, E. P.: Cardiac output in man by a direct Fick method. Effects of posture, venous pressure change, atropine, and adrenaline, Brit. Heart J. **6**:33, 1944.
4. Warren, J. V., Brannon, E. W., Stead, E. A., and Merrill, A. J.: The effect of venesection and the pooling of blood in the extremities on the atrial pressure and cardiac output in normal subjects, with observation on acute circulatory collapse in three instances, J. Clin. Invest. **24**:337, 1945.
5. Shenkin, H. A., Cheney, R. H., Govons, S. R., Hardy, J. D., and Fletcher, A. G., Jr.: On the diagnosis of hemorrhage in man—a study of volunteers bled large amounts, Am. J. M. Sc. **208**:421, 1944.
6. Remington, J. W., Hamilton, W. F., Caddell, H. M., Boyd, G. H., Jr., and Hamilton, W. F., Jr.: Some circulatory responses to hemorrhage in the dog, Am. J. Physiol. **161**:106, 1950.
7. Holt, J. P.: Effect of plethora and hemorrhage on left ventricular volume and pressure, Circulation Res. **5**:273, 1957.
8. Guyton, A. C., Lindsey, A. W., Kaufman, B. N., and Abernathy, J. B.: Effect of blood transfusion and hemorrhage on cardiac output and on the venous return curve, Am. J. Physiol. **194**:263, 1958.
9. Sjöstrand, T.: Volume and distribution of blood and their significance in regulating the circulation, Physiol. Rev. **33**:202, 1953.
10. Weissler, A. M., Leonard, J. J., and Warren, J. V.: Effects of posture and atropine on the cardiac output, J. Clin. Invest. **36**:1656, 1957.
11. Lilienfield, L. S., and Kovach, R. D.: Simplified method for calculating flow, mean circulation time, and downslope from indicator-dilution curves, Proc. Soc. Exper. Biol. & Med. **91**:595, 1956.
12. Snedecor, G. W.: Statistical methods, Ames, Iowa, 1956, Iowa State College Press.
13. Johnson, S. R.: The effect of some anaesthetic agents on the circulation in man, Acta chir. scandinav., Suppl. 158, 1951.
14. Cobb, L. A., Ralston, L. A., and Bruce, R. A.: Relationships between stroke volume, cardiac output, and "central blood volume" in cardiac patients (Abstract), Clin. Res. **7**:99, 1959.
15. Rapaport, E., Kuida, H., Haynes, F. W., and Dexter, L.: The pulmonary blood volume in mitral stenosis, J. Clin. Invest. **35**:1393, 1956.
16. Cobb, L. A., Kramer, R. J., and Finch, C. A.: Circulatory effects of chronic hypervolemia in polycythemia vera, J. Clin. Invest. **39**:1722, 1960.
17. Hamilton, W. F.: The physiology of the cardiac output (The Lewis A. Connor Memorial Lecture), Circulation **8**:527, 1953.

The effect of "local" pH changes on blood flow in the dog

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Alteration in the metabolism of an organ is well known to affect local blood flow. Variations in tissue metabolism can also induce changes in pH. It seemed of interest to us to determine how important pH variations themselves are for "local" blood flow. Although the subject is by no means new, we could find no satisfactory answers to this question. Early workers in this field, using the Trendelenburg preparation in the frog,[1] the isolated rabbit ear,[2] and perfusion of the hind limb of the cat,[3] reported decreased blood flow after the administration of alkali. On the other hand, Kester and associates[4] and Deal and Green[5] found increased blood flow in the femoral artery of the dog after local injection of either acid or alkali. These authors did not correct the ionic composition and osmolarity of their solutions to that of blood nor did they give any information of the effect of prolonged infusion of different buffer solutions.

The purpose of this study was to determine the effect of "local" pH changes on peripheral blood flow when buffers were given by infusion over prolonged periods. Efforts were made to induce changes in local blood pH insufficient to provoke important "systemic" reactions, to avoid changes in osmolarity and concentration of sodium in the blood, and, finally, to obtain some information of the mechanism of action of acid and alkali on vessels.

Methods

Mongrel dogs weighing 8.0 to 17.4 kilograms and anesthetized with sodium pentobarbital (30 mg./Kg. intravenously plus 15 mg./Kg. intramuscularly) were used in these experiments. The glycine-alanine-phosphate buffers were adjusted to the desired pH, and modified slightly so that at each pH they contained about 140 mEq. of sodium and of 330 miliosmol. After the administration of 4 mg./Kg. body weight of heparin sodium (1 mg. = 130 U.S.P. units), a needle was inserted into the femoral artery. Except where stated otherwise, buffers were infused through this needle at a rate of 4 ml. per minute. The sequence in which buffers at different pH's were administered was varied. Blood pH was determined by using a radiometer within 30 seconds of the withdrawal of blood samples. Blood flow in the majority of these experiments was determined by venous occlusion plethysmography. A plethysmograph of suitable size, and composed of Plexiglass, was placed around the hind limb above the knee of the dogs, so that both "muscle" and "skin-vessel" territory

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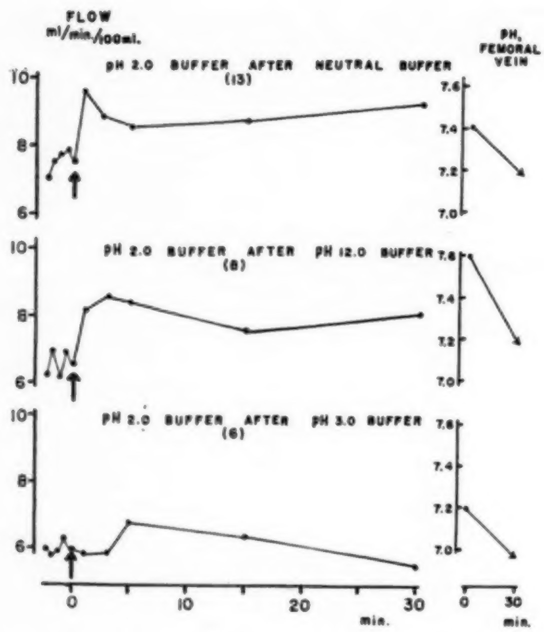

Fig. *1*. Effect of infusions of pH 2.0 buffer on blood flow in the femoral artery and pH in the ipsilateral femoral vein of the dog. Control flows are represented by the points to the left of the arrow which marks the start of the infusions. The number of animals in each group is given in parentheses.

were examined. The plethysmograph was filled with air and sealed with insulating putty.* The outlet from the plethysmograph led to a high-sensitivity Sanborn microphone. A calibration system utilizing a 0.5-ml. syringe was built into the tube leading from the plethysmograph to the microphone. Records were obtained from a Sanborn Twin Viso-Cardiette utilizing a Sanborn electromanometer. Paper speed was 25 mm. per second. Venous occlusion cuffs of different size, depending on the size of the animal, were inflated suddenly from a pressure reservoir. For occlusion the pressure which gave the highest flow value for each animal was employed. This was found to be preferable to utilizing an arbitrarily fixed pressure. Blood flow was registered at least four times prior to each infusion, then each minute for 5 minutes, and at least three times at 5-minute intervals thereafter.

In 6 experiments, blood flow was measured by the method of Girling[6] in the femoral and carotid arteries. This method utilizes a double cannulation of the artery. The proximal cannula leads into a small chamber separated from an ink-writing mercury manometer by a slack rubber membrane. The distal cannula leads from this chamber back into the artery. When the proximal plastic cannula is occluded for a short period (2 seconds in our experiments), the pressure in the manometer transmitted through the rubber membrane causes the blood in the chamber to flow into the distal artery at a rate dependent on the resistance in this artery. The result is a fall in the pressure record proportional to the blood flow at the site of cannulation. The blood flow can then be calculated from the magnitude of the pressure drop, the cross-sectional area of the manometer tube, and the duration of the occlusion.

In a further 7 experiments on dogs, maintained by artificial respiration, the effects of respiratory acidosis or alkalosis was studied. These changes were produced by changing the stroke volume and rate of a Bodine respiratory pump.

Results

In the first experiments, attempts were made to introduce acid and alkali buffers in an amount sufficient to alter pH in the observed vascular area, but insufficient to produce changes in blood pressure, heart rate, or respiratory rate in the animal. In 3 dogs the intra-arterial infusion of pH 2.0 or pH 12.0 buffers during a period of 90 minutes at the rate of 4 ml. per minute caused little change in heart rate, blood pressure, or electrocardiogram, although after infusion of acid buffer the pH in the ipsilateral femoral vein was reduced by at least 0.2, and after alkaline buffer it was increased by at least 0.2. Respiratory rate was slightly elevated by infusion of pH 2.0 buffer and decreased by infusion of pH 12.0 buffer. However, in a larger series of animals (26 dogs), respiratory rate after 30 minutes of infusion of these buffers was not materially affected.

In 12 dogs the pH changes were registered simultaneously in both femoral veins during the intra-arterial infusion of pH 2.0 and pH 12.0 buffers. As expected, pH changes on the side of the infused artery were consistently greater than in the contralateral vein. On the side of infusion, acid buffer decreased the control blood pH by 0.27, whereas by only 0.09 in the contra-

*Tremco Strip-Seal, Tremco Manufacturing Company, Canada.

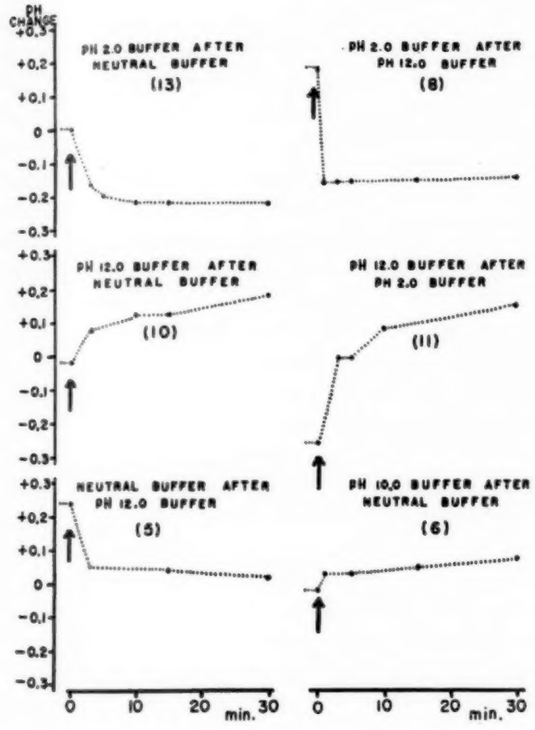

Fig. 2. Alteration of femoral vein pH by the infusion of buffers of different pH in the ipsilateral femoral artery. The start of infusion in each case is marked by an arrow. The number of animals in each group is given in parentheses.

lateral vein. The corresponding effects of alkaline infusion were 0.31 and 0.07. These findings support the contention that the pH changes in our experiments could be considered as mainly "local."

The infusion of *pH 2.0 buffer*—which was of course markedly diluted in the vessels by blood—caused an increase in blood flow (Fig. 1). When this was given after an infusion of a buffer adjusted to the individual control venous pH of the dogs ("neutral buffer"), the increase in blood flow was quite marked at the first minute of infusion. When 4 ml. per minute of acid buffer was infused into the femoral artery of 13 animals, the increase in flow in the first minute was significant ($t = 3.70$; $p < 0.01$). As the infusion was continued, the average blood flow was reduced, but was still consistently elevated over the 30-minute test period. No significant difference was found between the 1- and 15-minute values. When pH 2.0 buffer was replaced by the neutral buffer, flow returned to control levels in about 5 minutes. In this group of dogs the average pH in the femoral vein on the side of the arterial infusion had decreased at the end of 30 minutes from 7.40 to 7.18. This alteration in blood pH was produced rather abruptly (Fig. 2).

In 9 animals, pH 2.0 buffer was infused at a rate of 1, 8, or 16 ml. per minute. These variations in the rate of infusion caused correspondingly smaller or greater changes in blood pH and increases in flow. Similarly, when 4 ml. per minute of *pH 3.0 buffer* was administered to 7 dogs, the augmentation of blood flow was less than that caused by pH 2.0 buffer infused at the same rate; under these circumstances the pH in the corresponding femoral vein was reduced from an average of 7.42 to 7.22. Indeed, in this small series the increase in flow was not significant in the first minute, and in the fifth minute of infusion, t was 2.50 ($p = 0.02$ to 0.05). It is notable that injections of buffers into the femoral artery at acid or alkaline pH's, when tested in 3 dogs with Girling's method, gave increases in flow, when expressed in maximal effect, quite similar to those reported by Kester and associates.[4]

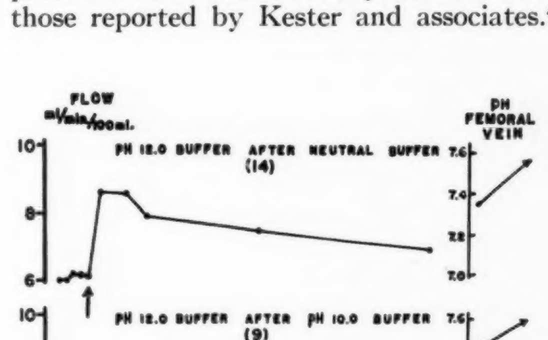

Fig. 3. Effect of infusions of pH 12.0 buffer on blood flow in the femoral artery and pH in the ipsilateral femoral vein of the dog. Control flows are represented by the points to the left of the arrow which marks the start of the infusions. The number of animals in each group is given in parentheses.

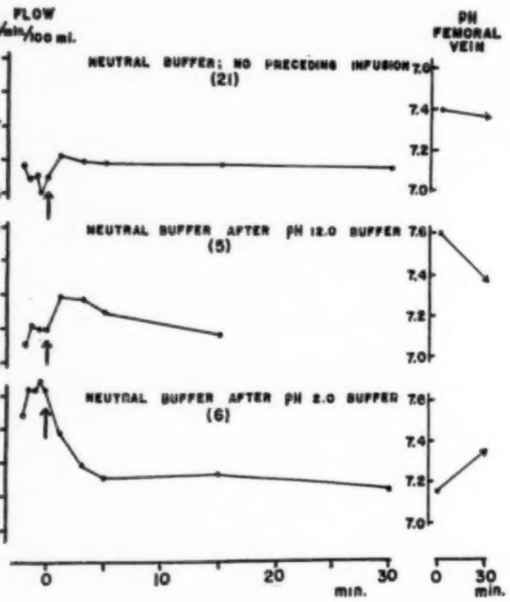

Fig. *4*. Effect of infusions of neutral buffer on blood flow in the femoral artery and pH in the ipsilateral femoral vein of the dog. Control flows are represented by the points to the left of the arrow which marks the start of the infusions. The number of animals in each group is given in parentheses.

However, the average increase in flow by Girling's method was considerably less.

To obtain information on the mode of action of acid on blood flow the sequence in which infusions were given was varied. In 8 animals, pH 2.0 buffer infused immediately after the infusion of pH 12.0 buffer caused a marked increase in blood flow (Fig. 1). Similarly, although less obvious in the first minute, the infusion of this buffer in 6 dogs was still effective after the previous administration of pH 3.0 buffer. On the other hand, infusion of pH 3.0 buffer, which was effective before pH 2.0 infusion, caused no increase in blood flow when it was given in the same dogs after 60 minutes of infusion of pH 2.0 buffer.

The infusion of *pH 12.0 buffer* after the administration of neutral buffer increased the blood flow. This augmentation in a group of 14 dogs (Fig. 3) was rather consistent and quite marked in the first minute, $t = 2.56$, $p < 0.01$. However, in contrast to infusion of acid, with continued infusion of alkaline buffer the blood flow was gradually reduced in most cases. After 15 minutes the increase in flow was no longer significant, as compared to control values. Indeed, in 5 animals in which infusion was continued over a period of 1 hour, average blood flow was lower at the end of this infusion than in the control period. Blood pH in the femoral vein on the infused side increased at the end of 30 minutes of infusion from 7.37 to 7.56. Repeated determinations of blood pH during the infusion in 10 dogs is shown in Fig. 2.

Infusion of *pH 10.0 buffer* to 11 dogs increased blood flow only slightly and blood pH from 7.36 to 7.47. Indeed, the increase in blood flow was not significant after 1 minute, and the average flow was still lower after 15 minutes of infusion.

Buffer of pH 12.0 caused an increase in flow in 5 dogs in which infusion followed the administration of pH 2.0 buffer, and also in 9 other dogs in which the infusion followed that of pH 10.0 buffer. On the other hand, pH 10.0 buffer in 5 animals increased flow after neutral buffer, but decreased blood flow when it was given after pH 12 buffer.

Neutral buffer was adjusted in each case to the control venous pH of the dogs as determined at the beginning of the experiments. In 21 dogs, neutral buffer caused only an insignificant increase in flow (Fig. 4). This elevation of blood flow could be explained by the extra volume added to the femoral flow by the infusion of 4 ml. of fluid per minute. The augmentation in flow produced by neutral buffer after infusion of pH 12.0 buffer was not statistically significant. On the other hand, after pH 2.0 buffer, flow was markedly reduced in 5 out of 6 dogs in the first minute after the infusion of neutral buffer (Fig. 4).

To determine how pertinent these results would be when applied to another vascular territory, blood flow was measured during 15 minutes of infusion of pH 2.0 and pH 12.0 buffers into the common *carotid artery*, about 5 cm. below the arterial bifurcation. For the sake of comparison, blood flow was also obtained in the femoral artery by the method of Girling, using double cannulation. Blood flow was increased less in the carotid artery than in the femoral artery during the infusion of acid or alkaline buffer; however, the difference between the responses in the two arteries was not significant. The method of Girling registers

not only flow but also pressure in the cannulated artery. From experiments using this method we learned that the local arterial pressure, femoral or carotid, was slightly but consistently decreased during infusion of acid or alkali. As a consequence, peripheral resistance was more decreased by the infusions than was indicated by the increases in flow alone.

The role of the *nervous system* in the vascular response to acid and alkaline buffers was studied in additional animals. In 7 dogs the effect of infusion of pH 2.0 and 12.0 buffers into the femoral artery was studied before and after acute denervation. While the dog's leg remained in the plethysmograph and the needle in the femoral artery, the sciatic and femoral nerves were sectioned and a periarterial denervation was performed. No differences were observed in the increases in flow caused by alkaline buffer before or after denervation. However, acid buffers failed to cause increases in flow in 5 out of 7 dogs after actue denervation. Because of the surgical manipulation necessary in this preparation, we were somewhat skeptical of the reliability of the flow values. Therefore, in 5 dogs, we investigated the effect of pharmacologic inhibition of the sympathetic and parasympathetic innervation on the above-described vascular responses. The increase in blood flow produced by pH 2.0 and pH 12.0 buffer was unaffected by the previous and simultaneous intra-arterial administration of 0.1 mg. per minute of atropine. However, pH 2.0 buffer caused less increase in flow after bretylium tosylate was given in a dose of 3 mg./Kg. intravenously. This effect in each of the 5 dogs was more pronounced at 90 minutes than at 30 minutes after the injection of bretylium tosylate, when the sympathetic nerve ends are known to be already markedly inhibited. On the other hand, in the same animals no consistent effect of bretylium tosylate was observed on the increase in blood flow caused by pH 12.0 buffer.

The effect of *respiratory* alkalosis or acidosis on the blood flow is by no means identical with that of the above-described metabolic alkalosis and acidosis. When venous pH was increased by at least 0.1 after 15 minutes of hyperventilation, blood flow in the hind limb decreased in each of 5 dogs. A decrease in pH of at least 0.1 produced by hypoventilation had a less consistent effect on blood flow.

Discussion

These experiments were designed to study the effect of infusions of acid and alkali on blood flow while avoiding the influence that these infusions might have on flow as a result of changes in osmolarity or in sodium gradient. Under these circumstances, the administration both of acid and of alkali increased blood flow in the femoral artery. A similar but less pronounced effect of these infusions was observed in the carotid artery. These results, in principle, are in agreement with those of Kester and associates,[4] Deal and Green's results[5] in the femoral artery, and the findings of McElroy and associates[7] in the coronary artery.

Since the pH of the blood is a very stable value, it was necessary to administer large volumes of the different buffer solutions in order to alter the blood pH. It is necessary, therefore, to consider the effect of the fluid volume itself in the interpretation of these results. In 3 dogs in which the effect of infusion of these large volumes on blood pressure, heart rate, and electrocardiogram was studied, no important alteration was observed in these parameters. Edema in the infused leg, even after infusions which lasted for several hours, was observed only rarely. Furthermore, the sequence of administration of the different buffers was varied in different animals so that interference as a result of expansion in plasma volume was minimized.

There was a direct relationship between the change from control blood pH, produced by the different types of infusions, and the increase in blood flow. The pH 2.0 buffer was more effective in increasing blood flow than the pH 3.0 buffer, and pH 12.0 buffer was more effective than pH 10.0 buffer. Similarly, neutral buffer was ineffective. These experiments indicate that it is the alteration from the neutral pH and not the absolute pH difference which is the trigger for an increase in flow. If this were not the case, then pH 12 given after pH 2.0 buffer, or pH 2.0 after pH 12.0 buffer, would have had greater effect than was observed; pH 3.0 after pH 2.0, or pH 10.0

after pH 12.0 buffer would have elevated the flow instead of decreasing it, and neutral buffer after pH 2.0 buffer would not decrease the flow.

Both acid and alkaline buffers reduced peripheral resistance. However, we believe that this does not mean that these two antagonists act in the same way on the vessels. The injection of acid caused a more prolonged increase in flow than did the injection of alkali. The increase in blood flow after alkaline infusion was gradually decreased while the infusion was continued, whereas the pH increase in blood was at least as great during the later stages of infusion as earlier. Acid infusion, on the other hand, had sustained action. Furthermore, pH 2.0 buffer after pH 12.0 buffer, and pH 12.0 buffer after pH 2.0 buffer still had marked effect. The results after acute denervation or after the administration of bretylium tosylate also suggest a difference between the mechanisms of action of acid and alkali. This difference might be explained by a better adaptation of vessels to alkalosis than to acidosis. In the effect of acid it seems probable from these experiments that the sympathetic nervous system is also involved. Whether the response of vessels to pH is secondary to changes in the blood pH, tissue pH, or pH gradient is unknown and must await further experimentation.

Respiratory alkalosis had an effect on blood flow opposite to that of metabolic alkalosis. These results correspond to those found recently by Patel and Gowdey[8] and could be explained by a depression in blood pressure during artificial hyperventilation.

Summary

Acid and alkaline buffers were administered by intra-arterial infusion at different pH's to dogs. Blood flow was measured with venous occlusion plethysmography, and in a few cases by arterial cannulation. Infusions were given affecting mostly the "local" pH, insufficient to cause major "systemic" reactions.

Both acid and alkali significantly increased blood flow in the femoral artery. This effect was less pronounced in the carotid artery.

When the sequence of the different buffers was varied, the response suggested that the difference from the control blood pH of the animals rather than the "absolute" differences was the factor causing increases in flow.

The sustained and more prolonged effect of acid infusions, the difference after denervation, and other results suggest different mechanisms for the action of acid and alkali on the vessels.

REFERENCES

1. Snyder, C. D., and Campbell, W. A.: Vascular reaction to epinephrine in perfusates of various hydrogen-ion concentrations, Am. J. Physiol. **51**:199, 1920.
2. Alpern, D.: Dependence of the contractile reaction of the peripheral vessels upon the hydrogen-ion concentration of the perfusion fluid, Pflüger's Arch. ges. Physiol. **205**:578, 1924.
3. Hemingway, A.: The sensitizing action of alkalies, J. Physiol. **62**:81, 1926.
4. Kester, N. C., Richardson, A. W., and Green, H. D.: Effect of controlled hydrogen-ion concentration on peripheral vascular tone and blood flow in innervated hind leg of the dog, Am. J. Physiol. **169**:678, 1952.
5. Deal, C. P., and Green, H. D.: Effect of pH on blood flow and peripheral resistance in muscular and cutaneous vascular beds in hind limb of pentobarbitalized dog, Circulation Res. **2**:148, 1954.
6. Girling, F.: Effect of intravenous and intra-arterial adrenaline, and of adrenaline after Priscoline, in hind limb of intact rabbit, Am. J. Physiol. **164**:400, 1956.
7. McElroy, W. T., Jr., Gerdes, A. J., and Brown, E. B., Jr.: Effect of CO_{21} bicarbonate and pH on the performance of isolated perfused guinea pig hearts, Am. J. Physiol. **195**:412, 1958.
8. Patel, Y. F., and Gowdey, C. W.: Changes in responses to catecholamines with changes in ventilation, Canadian Federation of Biological Societies, Third Annual Meeting, Winnepeg, 1960.

Monocusp aortic valvular prosthesis in dogs

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For diseased, calcified, stenotic, or insufficient aortic valves, replacement of one cusp with a prosthesis may bring a great improvement of hemodynamics. Total replacement may be the final goal, but substitution of only one leaflet is easier, and the results obtained may project some light on the problems that will be encountered with total replacement of the valve. This report describes the replacement in dogs of the noncoronary cusp of the aortic valve with a prosthetic cusp.*

Materials and preparation of valves

The materials used were knitted Teflon, polyurethane, Silastic (silicone rubber), and collagen with Dacron mesh. The monocusp valves were made on semilunar tricuspid molds patterned from a dog's aortic valve.[1] In making Teflon† and collagen† cusps, a small piece of the material was held between a male and female mold and cut out along the edge of the mold. Polyurethane† and Silastic† valves were made by dipping open molds in solutions of the plastic. The insertion lines of the valves were reinforced with braided Elgiloy† wire frames with 5 or 7 eyes; the Teflon valves were strengthened with a thick Teflon thread, and the collagen, polyurethane, and Silastic valves, with a thick Dacron thread. Polyurethane valves were siliconized with Siliclad† after the insertion lines were covered with polyurethane sponge. The insertion lines of Silastic valves were glued to Ivalon sponge by using a room-temperature vulcanizing Silastic†. These sponges serve for the ingrowth of fibrous tissues and prevent regurgitation around the valves. In order to reduce the time of insertion of the valve, 5 to 7 Mersilene 3-0 sutures (with double needles†) were attached to the insertion lines of the valves beforehand (Fig. 1) and were sterilized together with the valves in an ethylene-oxide sterilizer.

Methods

Twenty-three mongrel dogs, 19.4 to 28.9 kilograms in weight, were anesthetized with Nembutal. During the operation the circulation was maintained extracorporeally by a Foregger pulspirator.† The chest was opened through the fourth right intercostal space. The incision of the aortic wall was

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Received for publication Oct. 7, 1960.
*The first monocusp valves in our laboratory were made by Dr. M. Ionescu in 1958.
†Teflon: United States Catheter and Instrument Corp., Glens Falls, N. Y. Collagen: Ethicon, Inc., Somerville, N. Y. Polyurethane: B. F. Goodrich Co., Akron, Ohio (polyurethane V. C. 5CS1904). Silastic: Dow Corning Corp., Midland, Mich. (Silastic X-3-0146). Elgiloy wire frames: Elgin National Watch Co., Elgin, Ill. Siliclad: Clay-Adams, Inc., New York, N. Y. Vulcanizing Silastic: Dow Corning Corp., Midland, Mich. Double needles: Ethicon, Inc., Somerville, N. Y. (Mersilene = Dacron). Pulspirator: Foregger Co., Inc., Roslyn Heights, N. Y.

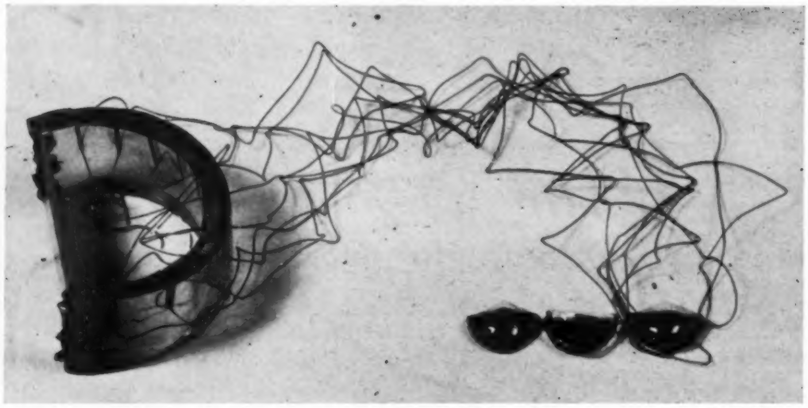

Fig. *1*. Monocusp aortic valves made of polyurethane. A strip of polyurethane sponge is glued along the fixation line on the ventricular side. In the right valve, five sutures with double needles are attached to it. The ends of the sutures are separately fixed in ten slits on the horseshoe ring (*left*) so that they will not become entangled.

somewhat curved; the lower end was stopped above the commissure between the posterior and right leaflets in order to prevent constriction of the noncoronary sinus by duplication in the suture line of the aortic wall. After the noncoronary cusp was excised, the artificial cusp was put in place. The sutures previously attached to the valve were brought to the outside of the aorta and tied there over a piece of Teflon felt (Fig. 2). In the last four experiments, aortic stenosis was created by sewing the right and the left natural leaflets together.

In order to prevent the formation of thrombus on the valve or to dissolve thrombi which might already exist, the following drugs were given to some dogs either separately or in combination: intravenous injections of 2,000 units of fibrinolysin per kilogram of body weight each day for 4 days; subcutaneous injections of 3.5 mg./Kg. of lipoheparin every 8 hours for 7 days; 300 mg. of nicotinic acid per day.

Ten cineangiocardiograms* have been taken in 9 dogs between 5 and 75 days after operation.

Results

Smooth polyurethane, Silastic, collagen with Dacron mesh, and knitted-Teflon valves were put in 16, 2, 2, and 3 dogs, respectively (Table I).

*Angiocardiograms were made by Dr. Shirey in the cardiovascular laboratory at the Cleveland Clinic.

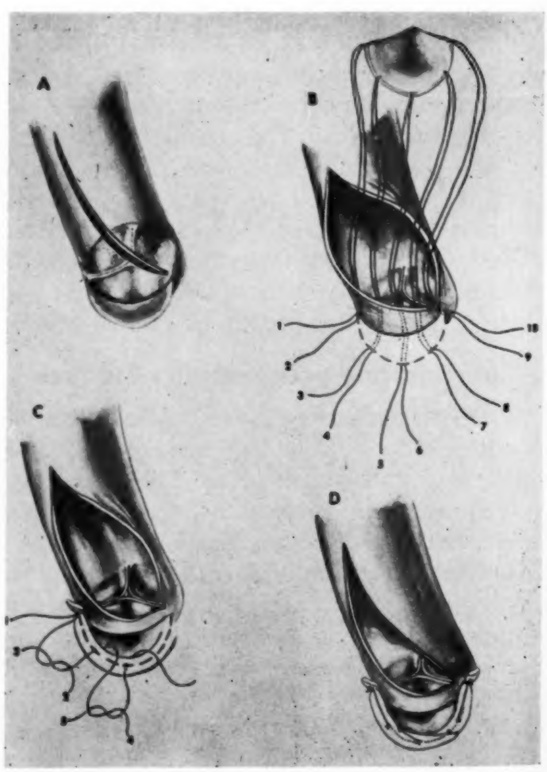

Fig. *2*. Insertion technique of the monocusp valve. *A*, Incision of aortic wall. Note that the lower one third of the incision is curved, pointing to the commissure between the right and the posterior leaflets. *B*, All sutures are passing out of the aorta along the bottom of the posterior leaflet, which has been removed. *C*, Fixation of the valve starts from the commissure between the left and posterior leaflets outside the aorta by tying the sutures over a piece of Teflon felt. *D*, Fixation of the valve is completed.

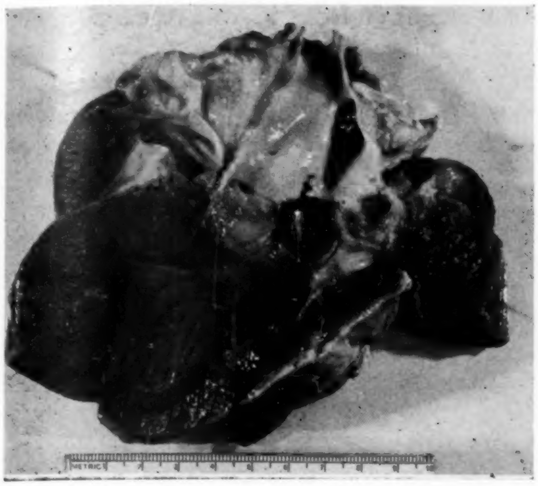

Fig. *3*. Smooth polyurethane monocusp in the dog sacrificed 130 days after operation. Note that the fixation of the valve is completely covered with endothelium which shows no sign of growing over the leaflets.

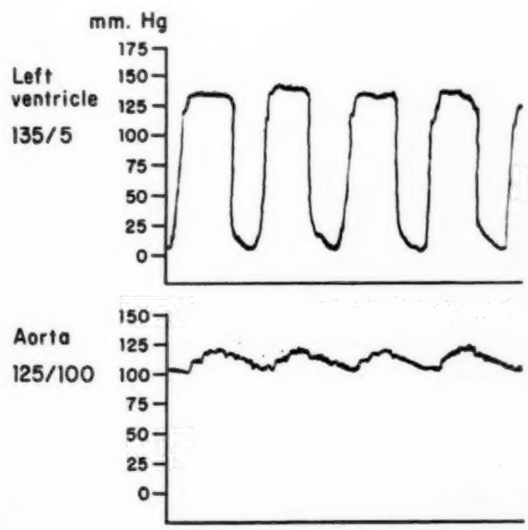

Fig. *4*. Pressure tracings in the left ventricle and in the aorta after implantation of an artificial monocusp and creation of stenosis by sewing together the two remaining natural leaflets. Note that the postoperative pressure gradient across the aortic valve is 10 mm. Hg.

One of 2 dogs with a Silastic valve survived 4 days before dying of aortic insufficiency caused by a tear along the fixation line of the valve extending to the bottom of the leaflet. The other died of occlusion of the left coronary ostium 4 days after operation. The sinus of the artificial leaflet was filled with thrombi. This corroborates earlier experience that Silastic is too weak to make thin leaflets and that it forms no safeguard against thrombosis.

One of 2 dogs with a collagen valve survived 15 days, but died of subacute endocarditis; the collagen cusp was collapsed and filled with thrombi. The other is alive 165 days after operation. In the angiocardiogram taken 45 days postoperatively the collagen cusp proved to be working, although a small amount of regurgitation was observed.

In 2 dogs with knitted-Teflon valves which survived 11 and 23 days, respectively, no thrombus was found. However, the Teflon cusp was shrunken, covered with fibrin, and in Dog No. 13 adhered to the right natural leaflet. This supports our previous experience with Teflon both in

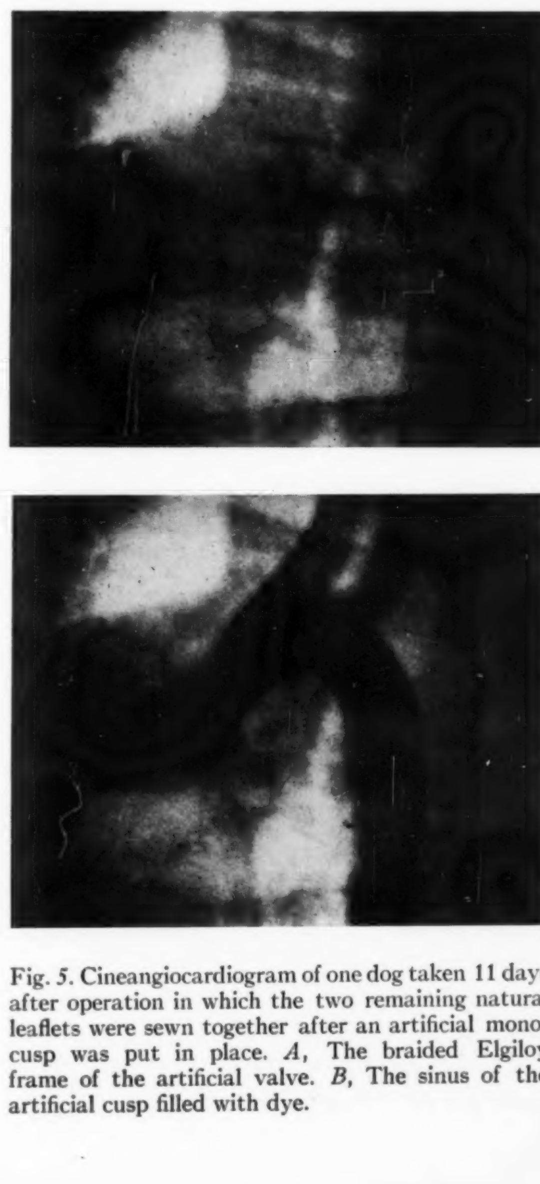

Fig. *5*. Cineangiocardiogram of one dog taken 11 days after operation in which the two remaining natural leaflets were sewn together after an artificial monocusp was put in place. *A*, The braided Elgiloy frame of the artificial valve. *B*, The sinus of the artificial cusp filled with dye.

experimental patches[2-4] and in mitral valves which indicates that this material will develop a layer of fibrin which disrupts or leads to a shrinking or growing together of the leaflets. Later, fibrosis occurs in the spaces between the Teflon fibers, and the valve stiffens.

Thirteen dogs with polyurethane monocusp valves survived longer than 2 days; 3 dogs are alive from 90 to 128 days, one of which has a thrombus according to the cineangiocardiogram; 10 died or were sacrificed. The polyurethane cusp was found to be filled with thrombus in 6 of the dogs. In all 3 dogs treated with fibrinolysin only, thrombosis was found. In the one dog treated with fibrinolysin, heparin, and nicotinic acid, and subsequently sacrificed 13

Table I. *Monocusp aortic valvular prosthesis in dogs*

Experiment number	*Body weight of dogs (Kg.)*	*Valve*			*Siliconization*	*Cardiac arrest (min.)*	*Fibrinolysin*	*Heparin*
		Material	*Edge*					
			Reinforcement	*Covering*				
1.	25	Smooth PU†	Braided Elgiloy wire	PU sponge	+	16		
2.	27	Smooth PU	Braided Elgiloy wire	PU sponge	+	20		
3.	23	Smooth PU	Braided Elgiloy wire	PU sponge	+	31		
4.	27	Smooth PU	Braided Elgiloy wire	PU sponge	+	23		
5.	28	Smooth PU	Braided Elgiloy wire	PU sponge	+	19		
6.	29	Smooth PU	Braided Elgiloy wire	PU sponge	+	18		
7.	22	Smooth PU	Mersilene thread	PU sponge	+	19	+	+
8.	21	Silastic	Mersilene thread	Ivalon sponge	−	20	+	+
9.	24	Silastic		Ivalon sponge	−	21	+	
10.	27	Collagen	Teflon thread		−	20	+	
11.	25	Collagen	Teflon thread		−	18		
12.	26	Knitted-Teflon	Braided Elgiloy wire		−	23		
13.	22	Knitted-Teflon	Teflon thread		−	28		
14.	22	Knitted-Teflon	Teflon thread		−	13		
15.	22	Smooth PU	Mersilene thread	PU sponge	+	21	+	
16.	23	Smooth PU	Braided Elgiloy wire	PU sponge	+	23	+	
17.	23	Smooth PU	Braided Elgiloy wire	PU sponge	+	27	+	
18.	20	Smooth PU	Mersilene thread	PU sponge	+	21	+	
19.	26	Smooth PU	Mersilene thread	PU sponge	+	30		
20.*	24	Smooth PU	Mersilene thread	PU + BH‡	−	28		
21.*	23	Smooth PU	Mersilene thread	PU + BH	−	32		
22.*	23	Smooth PU	Mersilene thread	PU + BH	−	27		
23.*	22	Smooth PU	Braided Elgiloy wire	PU + BH	−	23		

*Aortic stenosis was produced by sewing the two remaining natural leaflets together.
†PU: Polyurethane. Commercial sponge fixed with polyurethane V.C. (Estane, Goodrich).
‡BH: Barium heparin. This was used to prevent the formation of thrombus along the fixation line of the artificial monocusp. The ratio
Ivalon—polyvinyl alcohol, Clay-Adams, Inc., New York, N.Y.

days after operation, there was no thrombus in the sinus of the polyurethane cusp.

The over-all results indicated a high incidence of thrombosis in at least 7 of the 13 cases.

In 2 dogs (Nos. 2 and 18 sacrificed 130 and 82 days after operation, respectively) the valve fixation line on the ventricular side was completely covered with endothelium which did not grow over to the polyurethane leaflet (Fig. 3). Thus, no problem exists with smooth valve leaflets on the exposed, high-flow side of the valve leaflet.

It has often been noticed in a valve testing machine[5] that a leaflet stiffer than the other two does not move at all. The same thing may happen when the one

Table I. *Monocusp aortic valvular prosthesis in dogs*—Cont'd

Survived (days)	*Autopsy results*		*Cause of death*
	Artificial cusp	*Other parts*	
1	Leaflet too short	Pulmonary edema	Pulmonary edema
130	Filled with thrombus		Sacrificed
1/6	In place and all right		Myocardial damage
10	Filled with thrombus	Extensive intestinal necrosis due to mesenteric thrombosis	Peritonitis
8	Big thrombus	Saddle embolus in abdominal aorta	Multiple emboli
2	Big thrombus	500 ml. of bloody fluid in the chest	Bleeding in the chest
13	No thrombus	750 ml. of blood in the chest	Sacrificed
4	Leaflet torn; no thrombus	Pulmonary edema	Pulmonary edema
4	Filled with thrombus	One infarct in spleen	Occlusion of left coronary ostium with thrombus
15	Filled with thrombus	Pulmonary edema	Pulmonary edema
165 (alive)			Cineangiocardiogram; no thrombus; cusp shrunk somewhat
2	Collapsed and shrunken		Bleeding in the chest
11	Adherent to right natural leaflet	Right natural leaflet damaged	Aortic stenosis and insufficiency
23	Covered with thick fibrin; no thrombus		Myocarditis
11	Filled with thrombus	Two aortic natural leaflets damaged	Endocarditis
84	Filled with thrombus	Kidneys full of infarcts; saddle embolus in aorta	Multiple emboli
128 (alive)			Cineangiocardiogram; thrombus in cusp
82	Filled with thrombus		Sacrificed
1/6	In place	Abdominal cavity full of bloody fluid	Transfusion reaction
18	Filled with thrombus	Sutures for stenosis broken; aortic insufficiency	Pulmonary edema
95 (alive)			Cineangiocardiogram; no thrombus in artificial cusp
90 (alive)			Cineangiocardiogram; no thrombus in artificial cusp
31	Thin thrombus along the insertion line; no more than desirable	Two natural aortic leaflets covered with thrombi; extensive intestinal necrosis due to mesenteric thrombosis	Peritonitis

of barium heparin and polyurethane V.C. was 1:1 (Organon, Netherlands).

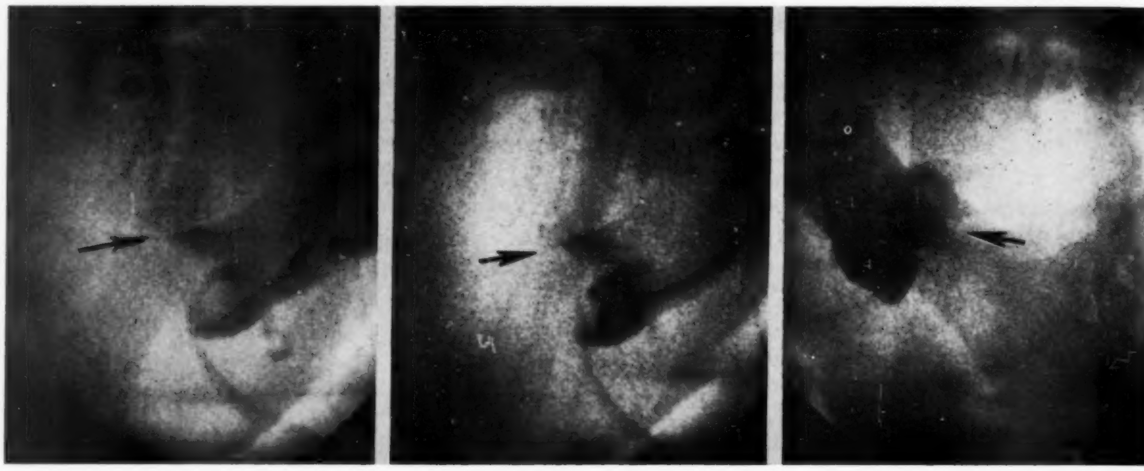

Fig. *6*. Cineangiocardiogram of Dog No. 22 (Table I), made 90 days after insertion of a monocusp valve and sewing together of the remaining natural valve leaflets. The artificial (noncoronary) cusp (*indicated by arrows*) is filled with contrast medium and is evidently not thrombosed.

artificial monocusp leaflet is stiffer than the two remaining natural leaflets. The lack of movement may promote the formation of thrombus under the artificial leaflet. In patients with aortic stenosis the rigid calcified leaflets are not movable. The artificial leaflet, therefore, has to move, and, as a result, the formation of thrombus may be prevented. In the last 4 dogs, stenosis was artificially produced by sewing the right and left leaflets together. A postoperative pressure gradient measured across the aortic valve in one such dog was 10 mm. Hg (Fig. 4).

A cineangiocardiogram taken 11 days after operation in one dog showed that the polyurethane cusp was moving (Fig. 5). The dog died 31 days postoperatively, and at autopsy an extremely thin thrombus was noticed firmly adhering along the insertion line of the polyurethane cusp. The sutured natural leaflets, on the other hand, were covered with irregular mushroom-like thrombi which presumably led to mesenteric embolization and death. The other dogs with the natural valve leaflets sewn together (Nos. 21 and 22; Table I) were more fortunate. Cineangiocardiograms made more than 90 days after insertion of the artificial cusps showed them to be free of thrombus (Fig. 6).

Discussion

Materials used in the experiments are conveniently divided into two categories: rough (collagen and Teflon) and smooth (Silastic and polyurethane). Collagen is the only material that is not only water repellent but even water absorbent. It is well accepted and pliable, but weak. The collagen provided by Ethicon is reinforced with Dacron mesh. Collagen with a finer Dacron mesh than that used in our experiments might be tried, although our experiences with collagen inserts in the atria showed extensive thrombosis. Teflon is inert and strong; nevertheless, it is not recommended as a material for artificial heart valves because it is inevitably covered with fibrin which becomes increasingly thicker. The fibrin finally makes the leaflets stiff or forms pseudoleaflets. In an autopsy of one of our experiments, we saw the Teflon leaflets grown together with the natural leaflets. These observations correspond with our experimental results in dogs having plastic patches in the heart chambers[2-4] and in dogs with artificial mitral valves. The water-repellent property of Silastic is advantageous, but because it has a tendency to tear under the high pressures in the left side of the heart, it is not recommended as a material in the making of artificial heart valves. If it were used, it should have a skeleton of a stronger material, such as Dacron mesh. Silastic, even if it did not tear, is no safeguard against the formation of thrombosis. Polyurethane, mentioned in another published paper,[1] is strong and can be siliconized

to make it more water repellent. In spite of our hopes, polyurethane leaflets would not stay open. Thrombi nearly always are formed in the sinus and originate from the insertion line of the artificial cusp. Since we forced the artificial leaflet to move by sewing the right and the left leaflets together, less thrombus was formed in the sinus of the artificial cusps.

The incision of the aortic wall in the earlier work was straight; it extended down into the middle of the noncoronary valvular sinus. This led to a reduction of the concerned sinus and a distortion of the inserted artificial valve. Presently, the aortic incision is curved, pointing at the commissure between the posterior and right leaflets. It does not enter the sinus proper, yet gives a sufficient view of the operative field. If the sutures on the outside of the aorta are tied over thick Teflon felt, valve cusps without a rigid frame are not distorted.

Administration of fibrinolysin alone to 6 dogs did not dissolve thrombi formed on the fixation line of the artificial valve cusp. A combination of fibrinolysin and heparin seemed beneficial in one dog (No. 7) which showed no thrombus after 13 days. The experiment was inconclusive in another dog, because, although there was no thrombus, the Silastic leaflet tore after 4 days (No. 8).

Conclusions

(1) Artificial monocusp aortic valves made of collagen, Teflon, Silastic, and smooth polyurethane were put into 23 dogs. (2) At first, the formation of thrombus or fibrin adhesion was noted in 14 dogs which survived longer than 2 days. Thrombosis occurred no matter what material was used, but not in 2 dogs which were treated with fibrinolysin and heparin. (3) Formation of thrombus originated from the insertion line of the artificial cusp in the sinus. (4) Cutting into the sinus proper can be avoided. (5) Rough materials promoted formation of fibrin on the cusps; smooth materials were better.

REFERENCES

1. Akutsu, T., Dreyer, B., and Kolff, W. J.: Polyurethane artificial heart valves in animals, J. Appl. Physiol. **14**:1045, 1959.
2. Mirkovitch, V., Akutsu, T., and Kolff, W. J.: Study of intracardiac thrombosis using plastic materials (Abstract), Physiologist **3**:114, 1960.
3. Kolff, W. J., Seidel, W., Akutsu, T., Mirkovitch, V., and Hindberg, J. R.: Rules for intracardiac thrombosis, Conference on Prosthetic Valves for Cardiac Surgery, Chicago, Sept. 9 and 10, 1960.
4. Mirkovitch, V., Akutsu, T., and Kolff, W. J.: Study of intracardiac thrombosis on plastics. Preliminary to the construction of artificial valves, J. Appl. Physiol. (Accepted for publication.)
5. Dreyer, B., Akutsu, T., and Kolff, W. J.: Testing of artificial heart valves, J. Appl. Physiol. **14**:476, 1959.

A study of arterial pressure plethysmograms and impedance plethysmograms

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In a previous communication in this Journal,[1] comparison was made between intra-arterial pressure pulses and pulses obtained from the same artery and site through a cutaneously applied cuff, short rigid tube, and strain gauge. It was observed that whereas the intra-arterial pulse is not affected by extensive changes in applied cuff pressure, the pulse recorded through the cuff becomes larger, usually up to systolic levels, and its contour is altered at the various cuff pressures.[2]

With the means at our disposal at that time no further comparison between the contours of the intra-arterially and extra-arterially recorded pulses could be made. It became apparent that this could be done only by a continuous plotting of the two pulse values against each other (e.g., through a subtracting amplifier), if the pulses to be compared were made exactly equal in size. This would further indicate the nature of oscillometric arterial pulsations as obtained with a variety of cuff systems used in clinical medicine today.

In addition, pulses recorded with the cuff and strain gauge (hereafter called *pressure plethysmograms*) have been compared to pulses recorded by amplifying impedance changes of the artery under study. Comparison of the data from these two methods would indicate the nature of pressure and impedance plethysmograms and their differences from pressure pulses of the same artery.

Subjects and methods

Fifteen healthy young males were studied under the same conditions described in the preceding paper[3]; in addition, 8 men with various cardiovascular disorders were similarly studied. All experiments were performed on the brachial artery, and the arm was held at the cardiac zero level. Pressure pulses were recorded as reported in the preceding paper.[3] Pressure plethysmograms from the same artery were obtained by placing a small cuff on the skin exactly over the tip of the needle and connecting it with a 15-cm. long PE-280 tube to another P23AA gauge. The air in the system could be subjected to any desired pressure up to 300 mm. Hg. The output of the gauge was fed into a transistorized DC-amplifier with a capacitor at its exit, so that its time constant was 1.8 seconds when connected to the Electronics for Medicine recorder; the natural frequency response of the plethysmographic amplifier was well over 100 cycles per second.

The pulses were made equal in size by adjusting the gain of the plethysmographic amplifier. They were then fed into the subtracting amplifier,[3] the pressure pulse

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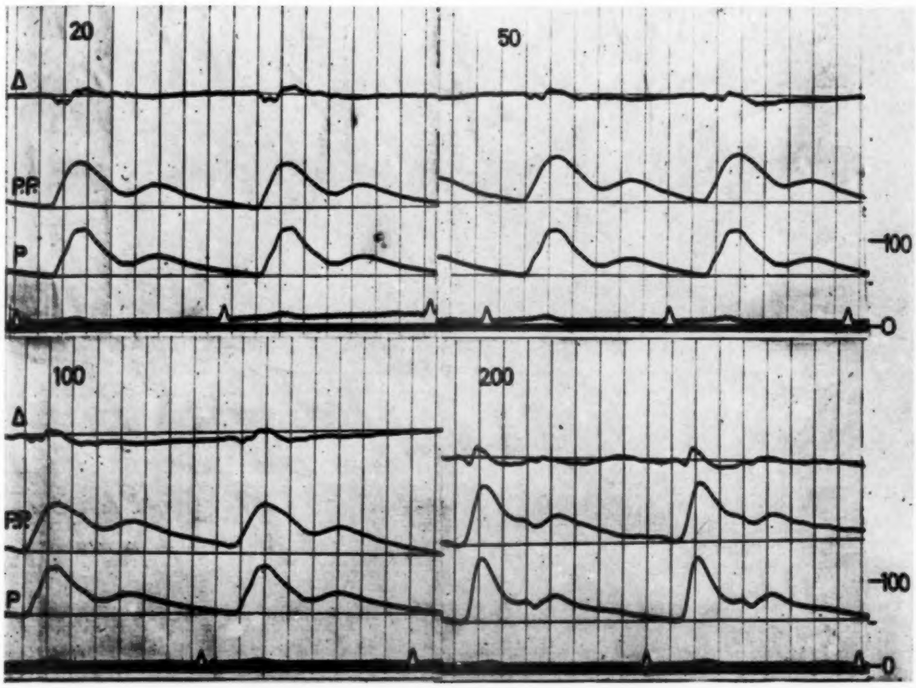

Fig. *1.* In each section, from below upward: intra-arterial pressure base line; electrocardiographic Lead II; left brachial arterial pressure (*P*); left brachial arterial pressure plethysmogram (*P.P.*, equalized in height to the intra-arterial pressure) obtained exactly over the tip of the Cournand needle. The top curve (Δ) is the instantaneous difference between pressure (positive) and pressure plethysmogram (negative). The numbers in each section indicate the applied cuff pressures, in mm. Hg; and at the right are the calibration levels for the intra-arterial pressure. Time lines in 0.1 second. Observe the constant difference in onset of the two pulses and the changes in pulse contours with the highest applied pressure (200 mm. Hg).

as positive input, and the pressure plethysmogram as negative input. The resultant subtraction curve was recorded along with the original pulses and ECG Lead II.

Arterial impedance (volume) pulses were recorded between the Cournand needle and a subcutaneous electrode close to the tip of the intra-arterial needle, or between two subcutaneous electrodes inserted on either side of the artery. In both cases the external cuff was positioned exactly over the impedance-recording electrodes; the subcutaneous electrodes were insulated except for their tips. The impedance amplifier was the same Parks unit employed in the preceding study.[3] The size of the impedance pulse was adjusted to equal exactly that of the pressure plethysmogram. The two pulses were fed into the subtracting amplifier, but with the pressure plethysmogram as positive, and the impedance pulse as a negative input. Recording of the pulses and their difference was done on the same multiple-beam recorder as reported above.

Results

1. Pressure plethysmograms versus intra-arterial pressure pulses. The pressure plethysmograms preceded the corresponding intra-arterial pressure pulses by a varying interval, constant in each case with normal sinus rhythm and under resting conditions. The subtraction curves were composed, therefore, of an early negative-positive deflection, representing the difference in arrival times of the fronts of the pressure plethysmogram and of the intra-arterial pressure pulse (Fig. 1, all four sections). Similar precedence of the impedance pulse with respect to the pressure pulse was described in the preceding paper.[3]

In about two thirds of the cases the subsequent course of the pressure plethysmogram obtained with very low cuff pressures (5 to 20 mm. Hg) was identical with the intra-arterial pressure pulse (Fig. 1, upper left); thus, the subtraction curve returned to its original base line after the early biphasic swing. In the other cases,

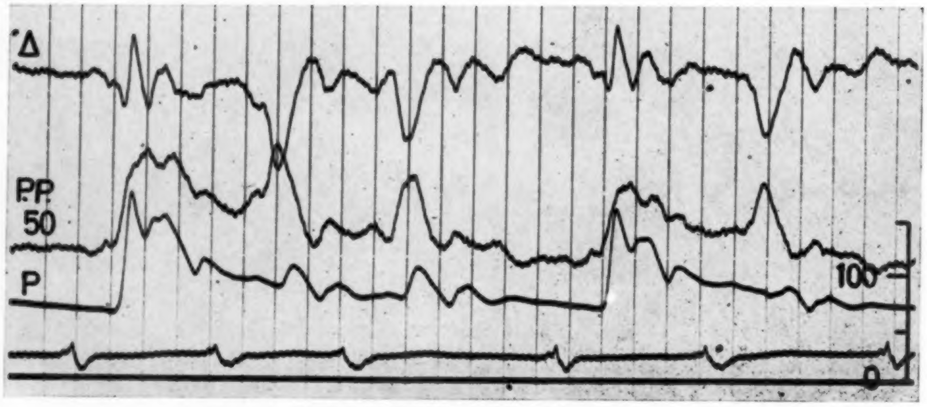

Fig. 2. As in Fig. 1, but electrocardiographic Lead I; from a young man with mitral disease, atrial fibrillation, and irregular ventricular rate. Observe the unequal height of the pressure plethysmogram compared to that of the intra-arterial pulses, and the variable transmission times of the two pulses.

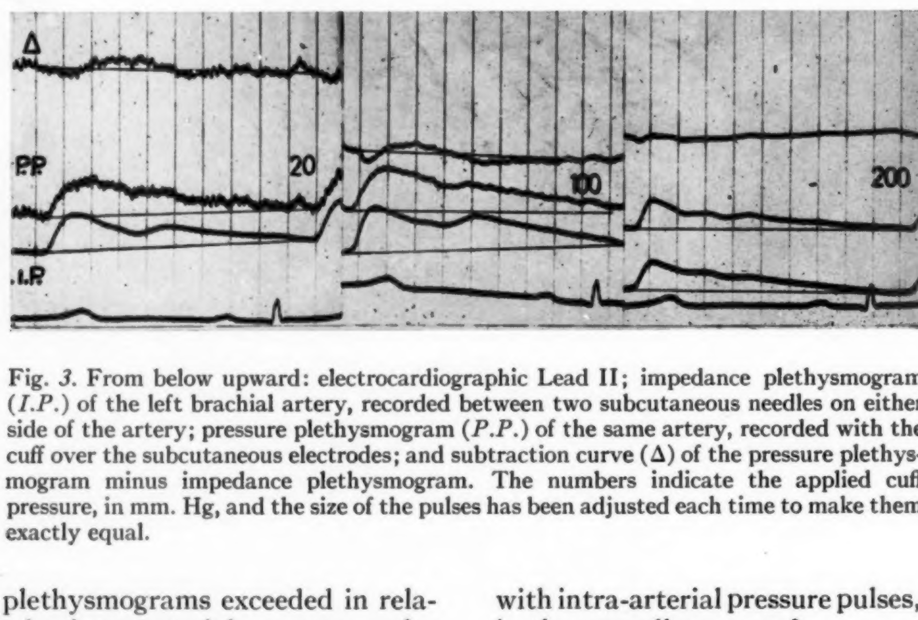

Fig. 3. From below upward: electrocardiographic Lead II; impedance plethysmogram (*I.P.*) of the left brachial artery, recorded between two subcutaneous needles on either side of the artery; pressure plethysmogram (*P.P.*) of the same artery, recorded with the cuff over the subcutaneous electrodes; and subtraction curve (Δ) of the pressure plethysmogram minus impedance plethysmogram. The numbers indicate the applied cuff pressure, in mm. Hg, and the size of the pulses has been adjusted each time to make them exactly equal.

pressure plethysmograms exceeded in relative size the intra-arterial pressure pulse throughout most of the cycle, so that the subtraction curve returned below its original base line after the initial deflection. Higher cuff pressures increased the size of the pressure plethysmogram, and to make it equal to the intra-arterial pressure pulse the gain had to be progressively reduced. Without exception, all such height-adjusted pressure plethysmograms exceeded in relative area the corresponding pressure pulses, so that the subtraction curves remained below the original base line for the most part of each cycle after the early negative-positive swing. This is exactly the relation obtained by a comparison of height-equalized impedance arterial pulses with intra-arterial pressure pulses, described in the preceding paper.[3]

Cuff pressures exceeding 100 mm. Hg partially impede the flow of blood at the recording site; the intra-arterial pulse becomes distorted with increased pulse pressure and faster upstroke and downstroke, like a peripheral pulse (Fig. 1, lower right); despite this, the relation of the plethysmogram to intra-arterial pressure is the same as with lower cuff pressures.

During extrasystolic arrhythmias the pressure plethysmograms precede by varying distances the corresponding intra-arterial pressure pulses. Furthermore, the described constant relations of pulse sizes are disturbed, and marked beat-to-beat variation is observed. Multiple observa-

tions, as the one in Fig. 2, have indicated that the relative height of the pressure plethysmogram with respect to the intra-arterial pressure pulse increases with increasing diastolic pressure at the time of the ectopic beat. Similarly, the difference in onset of the two pulses seems directly related to the existing intra-arterial pressure. Such observations suggest that the pressure plethysmograms are records of changes in diameter, which may or may not be accompanied by perceptible changes in intraluminal pressure during similar disturbances of the cardiac rhythm.

2. Pressure plethysmograms versus impedance arterial pulses. In contrast to the above-mentioned variable relations, no major differences in contour between arterial impedance pulses and pressure plethysmograms have been observed; the only noteworthy difference was a relatively faster rise (not onset) of the impedance pulse in most cases. Apart from this, there was no trend in the minor differences in contour encountered, over the wide range of cuff pressures tested per individual. Fig. 3 indicates the differences in contour between the impedance plethysmogram and the pressure plethysmogram of the same brachial artery, when the cuff pressure was raised from 20 to 200 mm. Hg.

Fig. 4 further emphasizes the essential similarity of the two pulses; it was obtained from a young man with mitral disease and atrial fibrillation, and the ventricular rate varied widely from beat to beat; despite the remarkable variability in pulse rate, size, and contour, the recorded pulses with the two methods are almost identical, and the slight differences were not accentuated when the cuff pressure was raised from 50 to 150 mm. Hg.

Discussion

The nature of the tracings obtained by "pressure plethysmographic" techniques is a subject of both theoretical and practical interest. Such techniques have been used since the early years of this century (see the review by Frey[4]), and are still widely used in oscillometry today.[2,5,6] It should be known, therefore, whether the recorded pulsations bear any similarity to the variations in intramural pressure or to transverse vibrations of the arterial wall. From the practical point of view, if pulses recorded by such a method bear a constant relation to either pressure or volume pulses, such a

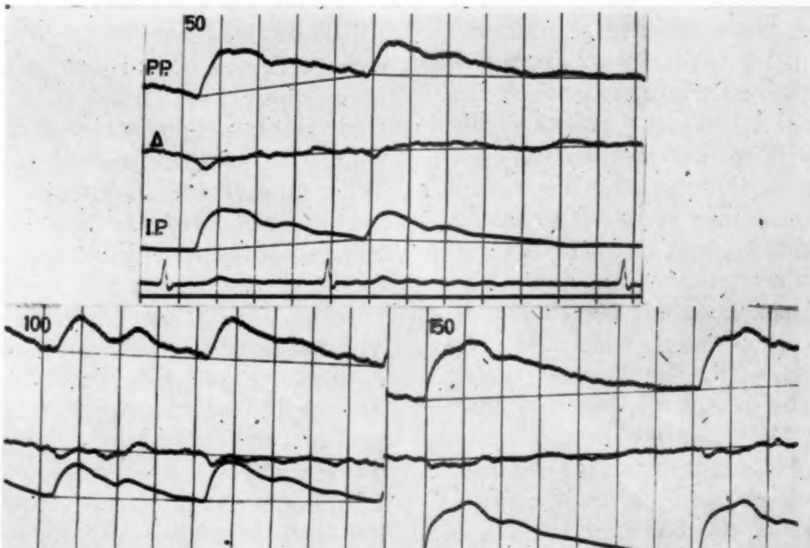

Fig. 4. As in Fig. 3, from a young man with mitral disease, atrial fibrillation, and variably slow ventricular rate. The impedance pulse is recorded between a Cournand needle and a small skin electrode over the tip of the needle; the subtraction curve is in the center in all three sections. Time lines in 0.2 second.

technique would have practical advantages over the more cumbersome arterial puncture or subcutaneous impedance plethysmography (for recording pressure and volume pulses, respectively).

The results herein indicate that pressure plethysmograms have contours identical to intra-arterial pressure pulses only at cuff pressures less than 20 mm. Hg; inasmuch as at such low pressures the gain of the amplifiers has to be quite high and baseline stability is poor, this similarity is mainly a matter of theoretical interest. For practical purposes it is important to note that over a wide range of cuff pressures the recorded pulses are changes in volume, because: (a) their onset precedes that of the pressure pulse, much as arterial impedance (volume) pulses do; and (b) their contour has the same relationship to the arterial pressure pulse contour from the same locus as does a purely volume pulse (see preceding paper[3]).

On the other hand, comparison of pressure plethysmograms with arterial impedance pulses obtained with the technique described in this and the preceding paper indicates that only minor differences exist; these are not accentuated with increase in cuff pressure or during arrhythmias. Such differences are probably related to the dissimilarity of the recording techniques; in fact, the impedance plethysmogram will record any resistivity change between the two electrodes, whereas the pressure plethysmogram will record mainly outward arterial expansion underneath the area of the cuff. It is likely that resistivity changes may occur without gross outward arterial expansion. If these inconstant differences in contour are disregarded, the similarity between pulses obtained with the two methods indicates that each method can substitute for the other and that they both record changes in arterial volume.

It is debatable whether tracings obtained with older methods, such as the "Spiegelsegmentkapsel" of the German authors of the twenties,[4] can be classified into the low-cuff-pressure or high-cuff-pressure types of pressure plethysmograms; an equally important factor altering the contour of the recorded pulses is the frequency response of the optical segment, or of the totality of the components of the modern cuff systems, tubing, amplifiers, and end recorders. In a photographic and aneroid system such as the one employed in this study, the only moving mass is the diaphragm of the transducer; as long as the dry mechanical resonance of the transducer is several hundred cycles per second, the response can be said to be flat to at least 20 per cent of the natural frequency.[7] High-frequency oscillations approaching the natural frequency of the gauge and inducing artefacts from resonance are not expected to occur in the system under study, and, indeed, impedance plethysmograms able to record much faster oscillations are devoid of them.

Summary

1. Comparison of contours of the following *height-equalized* pulses from the brachial artery has been made: (1) an intra-arterial pressure pulse versus an external pressure plethysmogram; (2) a pressure plethysmogram versus an impedance plethysmogram. Fifteen healthy young men and 8 men with cardiovascular disease were studied in this manner.

2. *Intra-arterial pressure pulses versus pressure plethysmograms:* At cuff pressures of 20 mm. Hg or less the contours by the two methods were identical in about two thirds of the cases; in the others the pressure plethysmograms were relatively larger throughout most of each cycle, even though their peak height was adjusted to equal that of the intra-arterial pressure pulse. With higher cuff pressures this relation became constant, i.e., all pressure plethysmograms had areas larger than those of the corresponding height-equalized pressure pulses. When pulses with unequal volume output were compared, as in the case of arrhythmias, the ratio of the pulse sizes with the two methods varied considerably. In every case the pressure plethysmogram preceded the corresponding intra-arterial pulse; this interval was variable and depended directly on the level of intra-arterial pressure at the moment of the ectopic beat.

3. *Pressure plethysmograms versus impedance plethysmograms:* Pulses obtained with either one of these methods were quite alike, and there was no trend in the minor differences in contour which were

occasionally observed, even when the applied cuff pressure was varied between considerable levels.

4. These data indicate that pressure plethysmograms and arterial impedance plethysmograms, obtained with the techniques described herein, are arterial volume pulses, and differ from pressure pulses recorded from within the same vessel. They may provide further information on the properties of the artery under study, in addition to the information obtained by methods of intra-arterial pressure recording.

REFERENCES

1. Dontas, A. S.: Comparison of simultaneously recorded intra-arterial and extra-arterial pressure pulses in man, Am. Heart J. **59**:576, 1960.
2. Kettner, M. G., Ferrero, C., and Duchosal, P. W.: Clinical investigation by the oscillogram of peripheral arteries, Am. Heart J. **49**:485, 1955.
3. Dontas, A. S., and Cottas, C. S.: Arterial volume and pressure pulse contours in the young human subject, Am. Heart J. **61**:676, 1961.
4. Frey, W.: Der arterielle und capillare Puls. *In* Bethe-Bergmann's Handbuch der normalen und pathologischen Physiologie, Berlin, Springer **7**:1223, 1927.
5. Daoud, G., Reppert, E. H., Jr., and Scott Butterworth, J.: Basal systolic murmurs and the carotid pulse curve in the diagnosis of calcareous aortic stenosis, Ann. Int. Med. **50**:323, 1959.
6. Karpman, H. L., Payne, J. H., and Winsor, T.: A practical, systematic laboratory approach to the study of the peripheral circulation, Ann. Int. Med. **53**:306, 1960.
7. White, G.: Response characteristics of a simple instrument, Statham Instrument Notes, No. 2 1948.

Contribution of the right ventricular wall to the QRS complex

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The extent to which the right ventricle contributes to the QRS complex is the subject of some disagreement.[1,2] Some conclusions concerning this contribution have been based on the changes in the early portion of QRS during right bundle branch block. Right ventricular depolarization, which normally occurs early in ventricular activation, is postponed until late in the QRS after experimental right bundle branch block. It follows that if the right ventricle contributes potentials to early QRS, the early as well as the late part of QRS should be altered when this bundle is blocked. Since all parts of QRS are altered after experimental right bundle branch block, it would seem that the right ventricle does contribute measurably to QRS. Clinical right bundle branch block, however, produces no abnormalities in the early QRS. Grant[2] compared electrocardiograms recorded during normal conduction and during right bundle branch block in the same individuals and found no alteration of early QRS. Sodeman and associates[3] found that the first part of the QRS was altered in only 2 of 23 patients with right bundle branch block. To resolve this conflict, Grant[2] postulates two types of clinical right bundle branch block. He feels that the more common type, in which the early part of QRS is unchanged, probably results from a peripheral block, and that the less common form, which is associated with alteration of the initial QRS, is due to a block of the right bundle.

Separation of the contribution of the right free wall alone from that of the right free wall *and* septum has rarely been attempted. In the only pertinent animal experiments, Boden and Neukirch[4] found definite changes in Lead II after they removed the free right ventricular wall from the perfused canine heart.

The purpose of the present investigation was to study the electrocardiographic contribution of the free right ventricular wall and that of the right septum. To demonstrate the contribution of the right wall, electrocardiograms were recorded before and after excision of the wall from (a) the perfused dog heart and (b) the dog heart in situ. To show the contribution of the right septum, the right bundle (in the perfused heart) was incised after the removal of the wall.

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Materials and methods

Excision of the right wall in the perfused heart. Ten hearts from mongrel dogs were perfused in a cylindrical plastic bath, 12 cm. in diameter and 13 cm. high. A donor dog provided the perfusing blood, which was maintained at 37°-39°C. The perfused heart was suspended from a Palmer vertical micromanipulator, which was used to raise and lower the heart. Electrodes were attached to the anterior, posterior, left, right, and bottom (apical terminal) of the plastic cylinder. An electrode attached to the aorta served as the top (basal) terminal. Unipolar leads were recorded between these terminals and a modified Wilson central terminal (indifferent lead). This central terminal was constructed by connecting each of the 6 electrodes through a 10,000-ohm resistor to a single terminal. Bipolar leads were recorded between the anterior and posterior, the left and right, and the bottom and top terminals.

Electrocardiograms were recorded on either a 12-channel Rycom oscilloscope, a 16-channel oscilloscope,[5] or an 8-channel Offner oscillograph. The film and paper speeds were between 50 and 500 mm. per second. Although more detail could be seen at the faster speed, 50 mm. per second was adequate for interpretation of changes in the direction of depolarization. Since the QRS is shorter in the dog than in man, the speed of 50 mm. per second produced QRS complexes roughly as long as those recorded at the conventional speed of 25 mm. per second in human subjects. To check the position of the heart at various times during the experiment, an artificial bipole was created on the surface of the heart by sewing electrodes in its apex and base and connecting them to a sine wave oscillator. The sine wave voltage was recorded from the electrodes attached to the surface of the cylinder. Any change in cardiac position would change these records. After the heart was placed precisely in the center of the perfusion cylinder, control electrocardiograms and control records of the oscillator voltage were obtained.

The heart was then elevated, and the free right wall was removed by cutting as close as possible to the septum and atrial border. After the heart was lowered to its preoperative position in the bath, the QRS complexes and the voltages from the oscillator were recorded. Since the tracings of voltages from the oscillator indicated that position of the heart could be precisely controlled with the micromanipulator, the use of the artificial bipole was thought to be unnecessary in the last 6 experiments. During these experiments the heart was positioned by direct measurement. As noted in Fig. 1, short recording time constants were at times used postoperatively in order to minimize the S-T displacement due to injury. This procedure did not alter the QRS complexes.

In order to determine what portion of a record was altered, a time reference voltage was recorded simultaneously with the electrocardiograms from the left ventricular wall. In the study of the records and the preparation of illustrations, the time reference voltages were placed vertically above one another.

In 4 experiments the right bundle was cut after removal of the right wall, and electrocardiograms were then recorded.

Substitution of a prosthesis for right wall in living dog. Acute experiments were performed on 2 mongrel dogs which weighed 10 and 13 kilograms. They were anesthetized with pentobarbital and maintained by artificial respiration. Four electrodes were sewn to the intercostal musculature in order to eliminate movement during the procedure. Unipolar potentials were recorded between the body surface electrodes and a modified Wilson central terminal. An Offner multichannel ink-writing oscillograph was used so that complexes could be studied during the procedure.

To determine whether thoracotomy alone might alter the electrocardiogram, preliminary control experiments were performed on both animals as follows. After preoperative control tracings were made, the thorax was opened by a mid-sternal incision, and the pleural and pericardial cavities were entered. The heart was manipulated and then returned to its previous position. The sternum and the overlying skin were then carefully approximated. A small opening was maintained in the middle of the incision so as to allow the air from the pleural space to escape while the lungs were inflated by clamping the outlet of the respirator. When all air appeared to have

been removed from the pleural space, the wound was closed completely and a second group of tracings was taken. Since the postoperative complexes were similar to those recorded preoperatively, the thorax was reopened and replacement of the free right ventricular wall was begun. A sheet of chamois the size of the wall was fastened with continuous silk suture to the borders of the free right wall. The wall was then removed through a large incision in the chamois while the venae cavae were occluded. The prosthesis was quickly closed with silk suture, and blood was removed from the pleural space. The thorax was again closed and the air it contained was expelled. A third group of tracings was then taken.

Results

These results will be discussed solely with reference to changes early in QRS. No consistent changes in any leads were noted late in QRS in this study.

Effects of excision of right wall from perfused heart.

RIGHT AND LEFT LEADS. Activity during the initial half of QRS was directed more leftward after the right wall had been removed in all 10 experiments. A typical result is illustrated in Fig. 1, *a* through *f*, and in Fig. 3. The control tracing from the right lead (Fig. 1,*a*) was positive-negative during the first half of the QRS complex. In the postoperative tracing (Fig. 1,*b*) the complex was negative throughout the first half of the QRS interval. Reciprocal changes appeared in the left unipolar lead. The control left lead (Fig. 1,*d*) was negative-positive during the first half of QRS, and the postoperative tracing (Fig. 1,*e*) was positive during the entire first half of QRS.

APICAL AND BASAL LEADS. In 9 of the 10 experiments the activity was directed more basally after removal of the wall. Sample records are shown in Fig. 1,*g* through *l*. In the control tracing from the apical lead (Fig. 1,*g*) the entire first half of QRS was positive. After the wall was removed, the amplitude of this potential was markedly reduced, and indeed the lead (Fig. 1,*h*) became positive-negative during the first half of depolarization. Reciprocal changes were seen in the basal lead. The potential was negative and then slightly positive during the first half of the QRS in the control tracing (Fig. 1,*j*). The postoperative potential (Fig. 1,*k*) was positive during this period. In the exceptional experiment there was no change of direction along the apico-basal axis. Inspection of the formalin-fixed specimen revealed that less of the wall had been removed from this heart than from the others. In a later experiment the wall was removed in two equal sections; typical changes in the apical and basal unipolar leads did not appear after removal of half of the wall but did appear when all of the wall was extirpated.

ANTERIOR AND POSTERIOR LEADS. In 5 experiments the postoperative activity was directed more posteriorly during the first half of QRS, and in the other 5 experiments the postoperative activity was directed more anteriorly. In the record shown, the control tracing from the posterior lead (Fig. 1,*m*) contains a small positive deflection and then a larger positive component during the first half of the QRS. In the postoperative complex (Fig. 1,*n*) the first half of QRS was initially moderately positive, then isoelectric, and then positive again. The control tracing from the anterior lead (Fig. 1,*p*) was positive during the first half of ventricular depolarization, and in the postoperative tracing (Fig. 1,*q*) the first half of QRS was negative. Activity, therefore, was directed more posteriorly after the wall was removed in this heart.

Right bundle branch block after excision of right wall from perfused heart. Although the QRS was prolonged after right bundle branch block, the early portion of QRS could be identified and compared with the early QRS under the preceding conditions. The direction of depolarization changed to the right after the bundle was cut. This happened in 3 of the 4 experiments. In the exceptional heart there was essentially no change. In both the right and the left lead, the complex after bundle branch block approximated more closely the control than the complex seen after removal of the wall alone. The changes shown in Fig. 1 are representative of this series of experiments. The first half of the QRS from the right lead (Fig. 1,*b*), which was negative after excision of the wall, became positive (Fig. 1,*c*) after the bundle was incised. In the left lead the change was from positive

(Fig. 1,*e*) to negative (Fig. 1,*f*) during the entire first half of QRS. After right bundle branch block, the projection of the potentials in the basal-apical direction was smaller (Fig. 3). The projections along the left-right and anterior-posterior axis were also smaller after the block. In the apical lead the early half of QRS was slightly more positive (Fig. 1) after than before the bundle was cut (Fig. 1,*h*). In the basal lead the QRS complex returned from a positive configuration (Fig. 1,*k*) to negative-positive (Fig. 1,*l*) after the bundle was cut. The activity was directed more anteriorly after incision of the bundle, as indicated in *m* through *r* of Fig. 1. This was not a constant finding; in 2 experiments, activity was directed more posteriorly during the first half of QRS. The changes during the latter half of depolarization were much smaller than those during the first half.

Substitution of a prosthesis for free right wall in situ. The complexes recorded after simple thoracotomy and closure differed very little from the preoperative control tracings. For the lead *most* changed by the thoracotomy, there was a correlation of .92 between the complexes before and after the thoracotomy. After removal of the wall, early depolarization was directed more toward the left in both animals (Fig. 2). Preoperatively, the first half of the QRS in the right lead (Fig. 2,*a*) was positive; the right lead was negative in early QRS after the chamois was substituted for the free right wall (Fig. 2,*c*). Reciprocal changes occurred in the left lead. During early QRS the left lead was more positive after (Fig. 2,*f*) than before (Fig. 2,*d* and *e*) the wall was removed. The vector of depolarization was directed less toward the apex after the operation in both experiments. Potentials from the apical lead during the first half of QRS were more positive preoperatively (Fig. 2,*g*) than postoperatively (Fig. 2,*i*). The initial part of

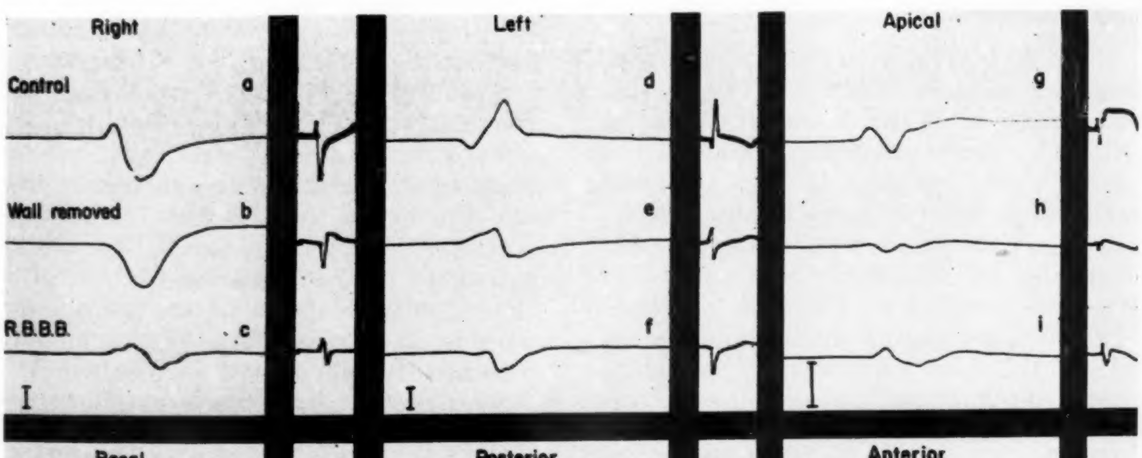

Fig. *1*. Typical electrocardiograms from the cylinder containing the perfused heart. Labels indicate the normal records and those taken after removal of the wall, and after removal of the wall and bundle branch block. Horizontal calibrations represent 50 milliseconds, and the vertical calibration represents 1 millivolt As indicated, records were aligned through the use of a left ventricular time reference potential. Discussion in text.

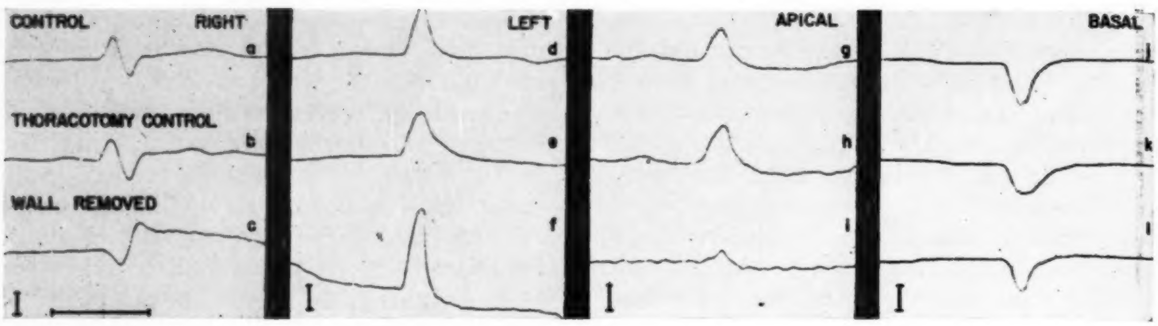

Fig. 2. Typical electrocardiogram from the body surface of the intact dog. Control before thoracotomy; thoracotomy control taken after thoracotomy had been repaired and air removed from chest; wall-removal record was taken after chamois had been substituted for the right wall. Horizontal calibration represents 80 milliseconds, and vertical calibration represents 1 millivolt. Discussion in text.

QRS of the basal lead was more negative preoperatively (Fig. 2,*j* and *k*) than postoperatively (Fig. 2,*l*). Thus, the changes in the QRS recorded at the body surface were very similar to those recorded from the cylinder when the wall was removed from the perfused heart.

Discussion

Plots of normal ventricular depolarization[5] indicate that the free right wall depolarizes from the inside out early in QRS. This inside-out depolarization, which begins in the apical portions of the wall, produces a wave of activity directed toward the right and toward the apex of the ventricle. In these experiments, activity after the removal of the right wall was directed more toward the left and basally during the first half of QRS, which is consistent with the picture of early depolarization.

During normal depolarization the right septum depolarizes from right to left and from apex to base.[5] If the right bundle is cut after the wall is removed, this right septal depolarization will be delayed. Therefore, the interruption of the bundle counteracts the effects of removal of the free right wall and tends to return the individual complexes toward normal configuration during the early portion of QRS. The complexes do not, however, return to the exact preoperative configuration. Thus, the contributions of the free wall and septum are not exactly equal and opposite. Furthermore, as can be seen in Fig. 3, the initial *vector* of depolarization is not returned to normal. Similarly, in experimental right bundle branch block,[6] when the early contribution of both the free right wall and the septum is delayed, the configuration of the early portion of the QRS is altered. It should be noted that the left-to-right contribution of the free wall is stronger than the base-to-apex contribution, as demonstrated by one experiment in which the base-to-apex change occurred only with removal of additional tissue.

The uncertainty regarding the normal contribution of the right wall can be attributed in part to the fact that it has not always been considered apart from the contribution of the entire right ventricle. Although there is a substantial amount of activity in the free right wall early in QRS, the magnitude of the potential produced by this activity is lessened by oppositely directed depolarization in the septum. Nevertheless, it does appear that functional loss either of the free right wall or of the free right wall and septum should be electrocardiographically detectable, but it is not necessarily true that the presence or absence of activity in either or both of these structures could be detected on the basis

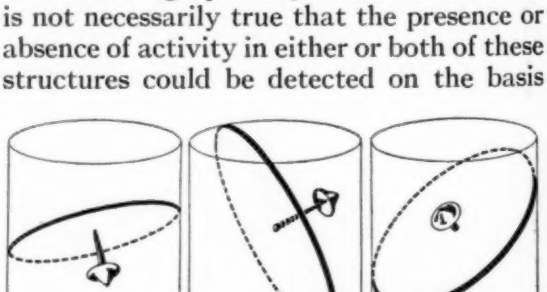

Fig. 3. Vectorial representation of initial direction of ventricular activation in the normal after removal of the right wall and after right bundle branch block.

of present standards for normalcy if no control tracing were available.

Although cutting the right bundle after removal of the free right wall does not duplicate right bundle branch block or any other known clinical lesion, this maneuver provides some information concerning right septal depolarization in the dog. When the bundle is cut after the wall is removed, the QRS complex is prolonged by about 12 milliseconds, between 25 and 33 per cent of the normal duration. It is thus clear that the right septum makes a sizable contribution to the QRS complex. This observation provides further evidence against the claim[9] that the septum depolarizes almost entirely from left to right. This finding does not limit the duration of right-to-left septal depolarization to 12 milliseconds, but this does appear to be a minimal duration of this phase of septal activity.

The study reported on in this paper can be considered an extension of the investigations of Jacobson and his co-workers,[7] who used plots of the normal ventricular depolarization to predict the electrocardiographic effects of lesions at various sites in the left ventricle. They then attempted to correlate these predictions with postmortem studies on individuals who had had myocardial infarcts; Jacobson and his co-workers considered the correlation adequate or good. Although the lesion which we produced does not occur clinically, the amount of the tissue removed was definitely known, so that changes were easily correlated with the plot of ventricular depolarization. Like the previous investigators, we believe that we found a good agreement between the actual and predicted effects of the lesions.

A significant finding during these studies was that thoracotomy alone does not alter the electrocardiogram if air is completely removed from the thorax. Similarly, Wilson and Meek[8] found that thoracotomy in acute canine experiments does not alter the bipolar limb leads. It follows that certain types of experiments which might superficially seem to require chronic experimentation can be acutely performed.

Our experiments leave unanswered two important questions. (1) Why is the early portion of QRS usually unchanged in the clinical syndrome characterized by marked prolongation of QRS with forces directed to the right late in the complex? (2) What types of lesions account for the clinical syndromes in which depolarization is somewhat prolonged but not so greatly prolonged as in experiments in which the right bundle is cut?

Conclusions

The direction of depolarization in the first half of QRS is directed more to the left and basally after removal of the free right ventricular wall in the perfused dog heart and in the intact dog. The right septum contributes significantly to the QRS, since cutting the right bundle after the wall was removed changed the first part of QRS.

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REFERENCES

1. Barker, J. M., and Valencia, F.: The precordial electrocardiogram in incomplete right bundle branch block, Am. Heart J. **38**:376, 1959.
2. Grant, R. P.: Clinical electrocardiography, New York, 1957, McGraw-Hill Book Company, Inc., pp. 119-123.
3. Sodeman, W. A., Johnston, F. D., and Wilson, F. N.: The Q_1 deflection of the electrocardiogram in bundle branch block and axis deviation, Am. Heart J. **28**:271, 1944.
4. Boden, E., and Neukirch, P.: Elektrokardiographische Studien am isolierten Saugetier-und Menschenherzen bei direkter und indirekter Ableitung, Pflüger's Arch. ges. Physiol. **171**:146, 1918.
5. Scher, A. M., and Young, A. C.: Ventricular depolarization and the genesis of QRS, Ann. New York Acad. Sc. **65**:768, 1957.
6. Erickson, R. V., Scher, A. M., and Becker, R. A.: Ventricular excitation in experimental bundle branch block, Circulation Res. **5**:5, 1957.
7. Jacobson, E. D., Rush, S., Zinberg, S., and Abildskov, J. A.: The effect of infarction on magnitude and orientation of electrical events in the heart, Am. Heart J. **58**:863, 1959.
8. Meek, W. J., and Wilson, A.: The effect of changes in position of the heart on the QRS complex of the electrocardiogram, Arch. Int. Med. **36**:614, 1925.
9. Medrano, G. A., Bisteni, A., Brancato, R. W., Pileggi, F., and Sodi-Pallares, D.: The activation of the interventricular septum in the dog's heart under normal conditions and in bundle branch block, Ann. New York Acad. Sc. **65**:804, 1957.

U vector loop or arc in normal subjects and in those with left ventricular hypertrophy

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Although most of the electrocardiographic deflections have been studied by vectorcardiography, we are not aware of any systematic study on the U vector loop or arc. This is because the U loop is very small and merges with the ST-T and P loops and the initial and terminal portions of the QRS loop. The method of differential vectorcardiography[1] has enabled us to study the morphology of the U loop. In this research the characteristic features of the U loop of the normal heart and of left ventricular hypertrophy were studied.

Materials and methods

U-loop vectorcardiograms were obtained from 61 subjects. These subjects showed a pulse rate of around 60 to 80 per minute. Those with a faster pulse rate were excluded because of the difficulty of dissecting the U loop. All subjects had a sinus rhythm. Of these, 30 were normal healthy subjects and the other 31 had left ventricular hypertrophy. Their ages and sex distribution are shown in Table I. Most of the former group were medical students and house officers. In the latter group the diagnosis of left

Table I. Age and sex distribution of all of our subjects

Diagnosis	*Sex*	*Age (years)*							*Total number of subjects*
		11-20	*21-30*	*31-40*	*41-50*	*51-60*	*61-70*	*71-80*	
Normal	Male	2	21	3	1	—	—	—	27
	Female	—	1	1	—	—	1	—	3
Left ventricular hypertrophy	Male	—	2	—	5	10	6	1	24
	Female	—	—	—	2	4	1	—	7

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ventricular hypertrophy, and mostly dilatation, was made on the basis of chest roentgenograms, conventional 12-lead electrocardiograms, and the results of physical examination, including determination of blood pressure, in each subject. This group was composed of 23 cases of essential hypertension, 2 cases of renal hypertension, 1 case of mitral insufficiency, and 1 case of combined valvular disease. The other 4 subjects showed a complication of myocardial infarction and were excluded from this study, which sought for the vectorcardiographic features due to ventricular overloading itself.

Left ventricular hypertrophy was classified tentatively into three grades according to its severity. Grade I included the cases in which slight left ventricular enlargement was noted on the chest roentgenograms and by physical examination. The electrocardiograms either could not be said to show left ventricular hypertrophy or could be said to do so only after various measurements had been taken and checked with the criteria of left ventricular hypertrophy proposed by Sokolow and Lyon.[2] The cases in which only the roentgenogram or electrocardiogram revealed slight or moderate left ventricular hypertrophy were also included in this grade. Grade II included the cases in which moderate left ventricular enlargement was observed on the chest roentgenograms and by physical examination. The electrocardiograms in these cases showed sufficient evidence of left ventricular hypertrophy, but the findings indicated a moderate hypertrophy, not presenting the typical S-T segmental depression and T-wave inversion. The cases in which two of the three items, i.e., the roentgenogram, electrocardiogram, and results of physical examination, revealed moderate or fairly marked left ventricular hypertrophy were included in this grade. Grade III included the cases which showed marked left ventricular enlargement on the chest roentgenograms and by physical examination. The electrocardiograms in these cases revealed also marked left ventricular hypertrophy, showing S-T segmental depression and T-wave inversion. The cases in which all of the three items revealed moderate left ventricular hypertrophy were also included in this grade.

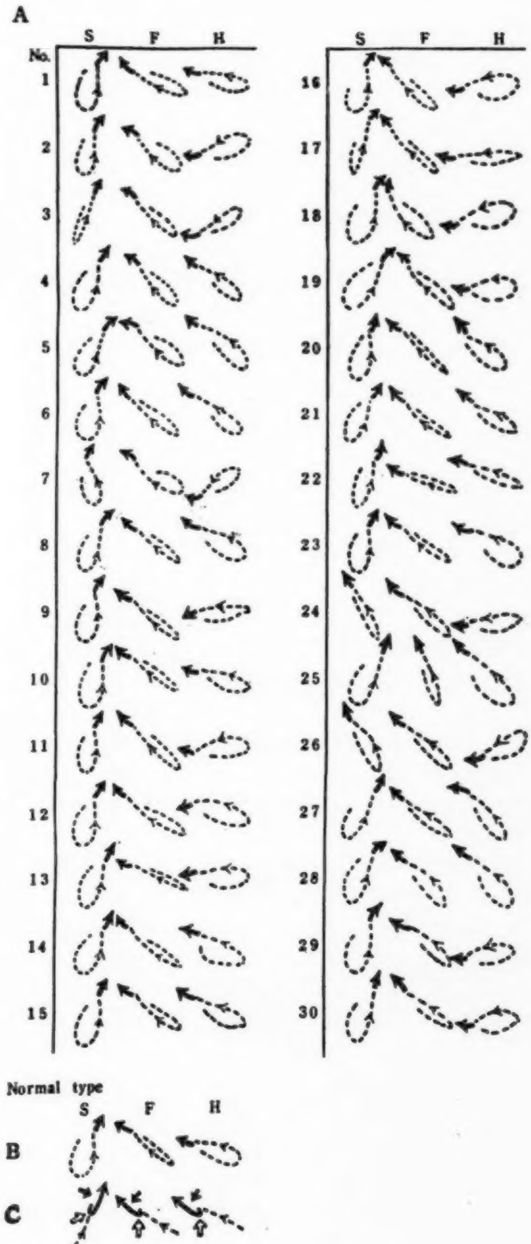


Fig. *1*. Diagrams of the T-U vector loops in all of our normal cases. Short solid lines with arrows on their tips show the U vector loops, and broken lines the T vector loops. Arrows indicate direction of inscription. Numbers show those of normal cases. *S*, Sagittal plane. *F*, Frontal plane. *H*, Horizontal plane. Almost all cases can be regarded as having a configuration such as that shown in *B*, which thus can be called the normal type. There were 7 exceptional cases, i.e., Case 24 through Case 30, which showed counterclockwise inscription of the T loop in the frontal plane. However, even in these cases the U loop does not look different from that of other normal cases. As for *C*, see text.

Table II. *T-U vector loop of left ventricular hypertrophy. Summary of features in all three planes and relationship to the severity of left ventricular hypertrophy*

Grade of left ventricular hypertrophy	*Normal in all planes*	*Abnormal T-U loop*		
		T loop concordant with QRS, including cases of abnormality in U loop only		*T loop discordant with QRS*
		Abnormal in one or two planes	*Abnormal in all planes*	*Abnormal in any one of planes*
I	0	0	1	0
II	1	9	4	3
III	0	1	1	6
Total number of cases	1	10	6	9

Vectorcardiograms were taken in all cases by the method proposed by Frank.[3] After the whole vector loop amplified at a magnification of 1 mv. to 0.7 inches was photographed, in each case, the monitor electrocardiograms of our dissecting apparatus[1] were dissected from the beginning of the T wave to the end of the U wave, and the corresponding part of the vector loop was amplified to the higher magnification of 1 mv. to 2.8 inches and photographed. This part of the vector loop will be called the *T-U vector loop* in this paper. Next, only the U wave was dissected and its loop was also photographed at this higher magnification. Three planar projections were always photographed at the same time. Simply taking pictures was not sufficient to reveal the direction of inscription of the U loop, and careful observation of the dissected U loop or T-U loop on the cathode-ray oscilloscope was usually necessary. The time-constant of our vectorcardiograph was arranged so as to be as long as 2.8 seconds, in order to avoid distortion of such minute loops.

Results

By means of dissection the U loop could be noticed after accumulated experience in all except one case, in which no definite direction of the beam-spot movement could be noticed because it was too minute.

After the T loop was inscribed, the beam-spot appeared to stay for a moment at the T-U junction, which corresponds to the T-U segment of the electrocardiogram; then the U loop was inscribed much more slowly than the T loop. Thus, the T-U junction was always clearly identified.

The U loop of normal subjects resembled a small, slightly curved club and was inscribed almost in the direction of continuation of the terminal limb of the T loop. Slight bending occurred, especially in the sagittal plane, at the T-U junction, differentiating the U loop from the T loop.

According to the configuration just described, a term such as *U vector segment*, or *U vector arc*, might be preferable to the term *U vector loop*. However, since none of the other components of the vectorcardiogram have been so called, even though, for instance, some abnormal ST-T loops are actually arc-shaped, the term *loop* was used in this paper.

The T loop of normal subjects was directed to the left, inferiorly, and anteriorly, or slightly posteriorly in its long axis. It was inscribed clockwise in the frontal plane and counterclockwise in the horizontal and left sagittal planes.

From a glance through the tracings of Fig. 1,*A*, all from the normal subjects of this study, it can be realized that the inscription of the U loop in continuation of the terminal limb of the T loop, together with the above-mentioned direction of inscription of the T loop, forms the characteristic feature of the normal T-U loop, which can be shown by the diagram in *B* of Fig. 1. (The vector loop from the beginning of the T loop to the end of the U loop is designated as the *T-U loop* in this

paper.) An example of this feature in a loop from a normal subject is seen in Fig. 2. Loops from all of our normal subjects showed this feature, except in 7 cases in which there was counterclockwise inscription of the T loop in the frontal plane. Even in these subjects the U loop was inscribed in continuation of the terminal limb of the T loop as in other normal subjects (Fig. 1,*A*).

When the end of the U loop is considered as the null point of the whole vector loop, the T-U junction vector, namely, the vector from the null point to the junction between the T loop and the U loop, was directed to the left, inferiorly, and mostly anteriorly. The distribution of this vector in normal subjects is shown in Fig. 3,*A*, in which the end points of these vectors were plotted, taking their magnitude into consideration.

It is shown that the vectors are distributed mostly in a certain limited extent, ranging from 0 to +90 degrees in the frontal and horizontal planes and from +90 to ±180 degrees in the left sagittal plane. In *A* and *B* of Fig. 3, only those cases in which the vectorcardiograms were well photographed were chosen for measurement, but the discarded cases showed a similar tendency.

Which point of the U vector loop corresponded to the peak of the U wave of the electrocardiogram offered a difficult problem. It could never be clearly identified. However, when the dissection was made from some points of the T wave to the peak of the U wave in the monitor electrocardiogram, the vector loop ended not far beyond the T-U junction, but rather close to it. Graphical derivation of the T-U loop from component electrocardiograms showed a slight return movement at the beginning of the U loop in many cases, as is shown in Fig. 1,*C*, where the tip of the return movement, indicated by white arrows, corresponds to the peak of the U wave. However, in none of our cases was such a return movement definitely visible on the actual cathode-ray oscilloscope or in the photographs. It was presumed that the apparent stay of the beam-spot at the T-U junction for a moment might be due to this return movement in some cases, which could be clarified at a magnification higher than ours. The fact that the T-U junction was

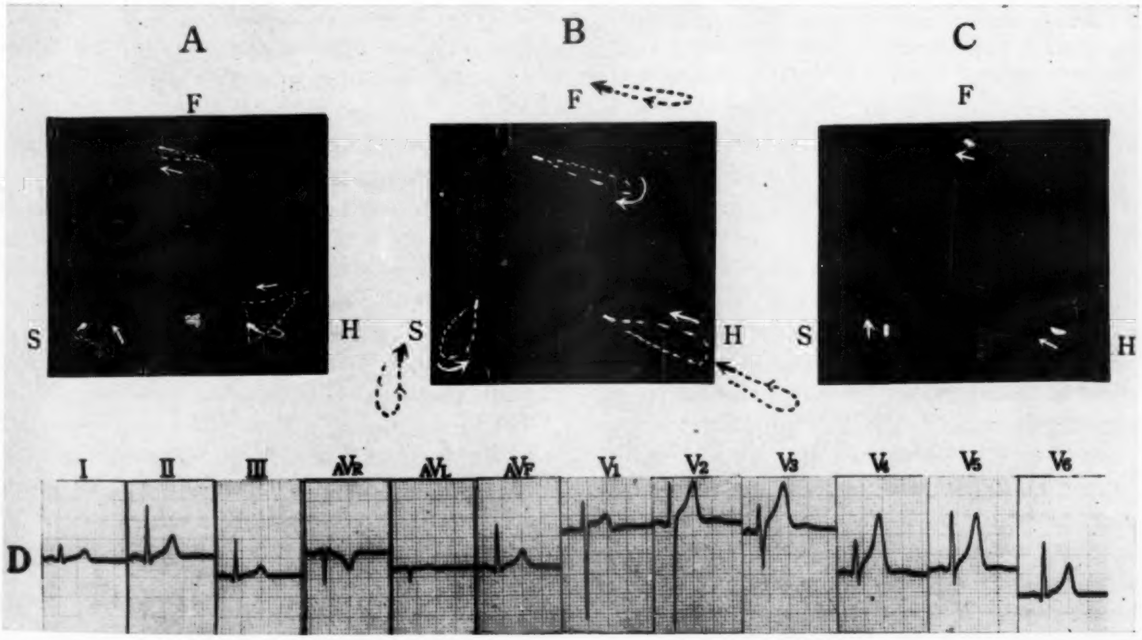


Fig. 2. An example of the T-U loop of a normal 29-year-old man. Arrows show the direction of inscription of the vector loop. *A*, The entire loop. *B*, The T-U vector loop dissected. In the diagram, short solid lines with arrows on one end show the U loop, and the broken lines show the T loop. *C*, Only the U vector loop was dissected. *D*, Conventional electrocardiograms taken at standard sensitivity. *F*, *S*, and *H* denote frontal, sagittal, and horizontal planes.

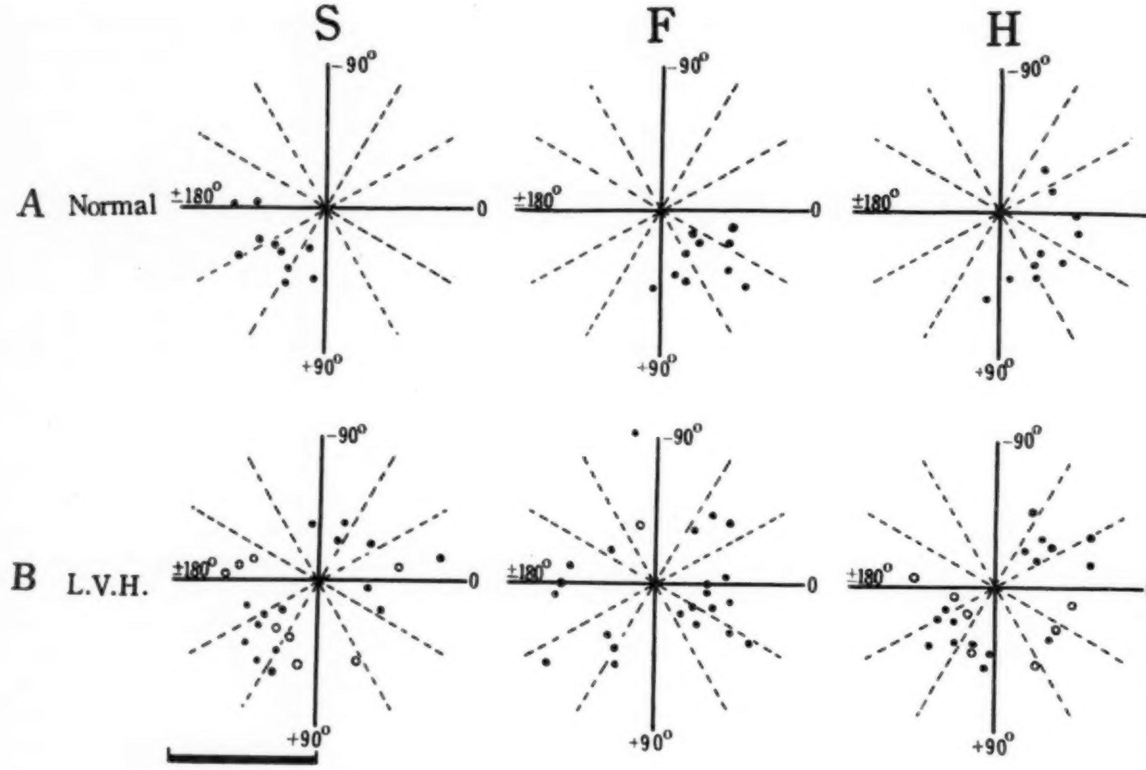


Fig. 3. Distribution of the T-U junction vectors of normal cases (*A*) and cases of left ventricular hypertrophy (*B*). When the T vector is discordant with the QRS vector, the T-U junction vector may have a significance different from that when the T vector is normal or concordant with the QRS vector, even if by chance both have the same direction. Therefore, the T-U junction vectors with the discordant T vector are indicated by open circles while others are indicated by closed circles. (For the purposes of this study, when the difference between the long axis of the T and QRS loops in a plane was more than or equal to 120 degrees, the T loop or vector was arbitrarily said to be discordant with the QRS loop or vector, and concordant when the difference was less.) A transverse bar at the left lower corner of the figure indicates the magnitude of 0.1 mv. *S*, *F*, and *H* denote sagittal, frontal, and horizontal planes.

so clearly identified may be due to this tendency. Anyway, since the point of the U loop, corresponding to the peak of the U wave, was close to the T-U junction, and since the recognized U loop was like a small, slightly curved club, the direction of the U vector, i.e., the vector from the null point to the point corresponding to the peak of the U wave, was presumed to be almost the same as the T-U junction vector.

In cases of left ventricular hypertrophy, on the contrary, the U loop began with a marked bend at the T-U junction and extended in various directions, resembling also a small curved club, but sometimes much larger than normal U loops. In Fig. 4, all the cases of left ventricular hypertrophy are classified according to the manner in which the U loop joined together with the features of the T loop in each plane, and two actual examples are shown in Figs. 5 and 6. Sometimes the U loop was inscribed as in normal cases in the continuation of the terminal limb of the T loop, but in such cases of left ventricular hypertrophy the T loop itself was abnormal, either in the direction of inscription of the loop or in the direction of its long axis, whether it was concordant or discordant with the QRS loop. Because of such bending at the T-U junction or of the abnormal direction of the long axis of the T loop, the direction of the T-U junction vector and the U vector was in many cases different from that in normal cases and was distributed widely, as is shown in Fig. 3,*B*. Thus, if the whole T-U loop is considered, few cases retained normal features as shown in Fig. 1,*B*. Actually, we could find only one case which retained normal features in all three of the planar projections among the 27 cases of left ventricular hypertrophy, as is seen in

Table II. In a few other cases, normal features were retained in one projection, whereas abnormal features were observed in other projections.

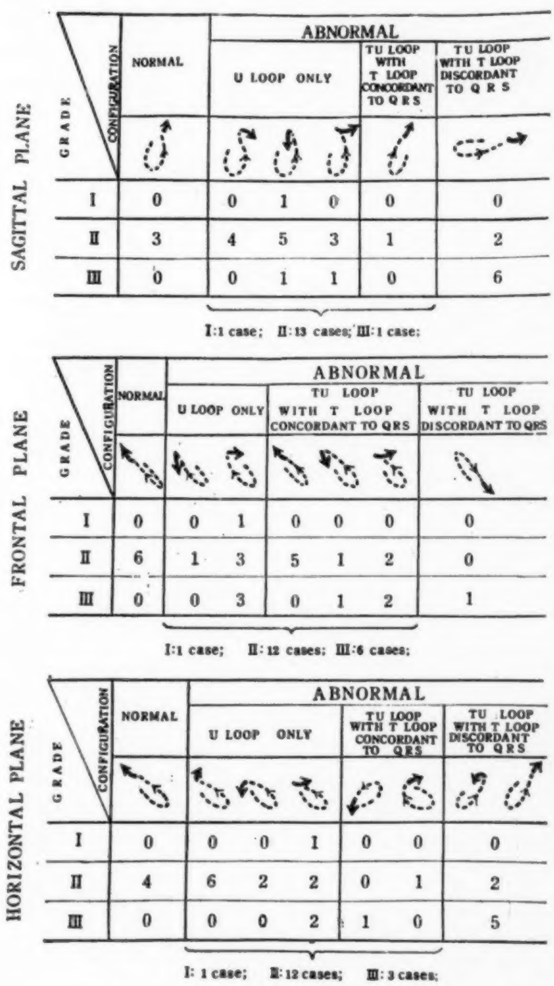
Furthermore, the following tendency can be observed from Fig. 4 and Table II: in the group of cases which retained normal features in any one of the planes, or which showed abnormality in the U loop only, or which showed abnormality somewhere in the T-U loop but had the T loop concordant with the QRS loop, there were more cases of relatively slight or moderate left ventricular hypertrophy; whereas in the group in which the T loop was discordant with the QRS loop there were more cases of relatively marked left ventricular hypertrophy (Fig. 6).

In our cases of left ventricular hypertrophy, 5 showed a negative U wave and 7 showed a negative T-U segment in the electrocardiograms. In all of these the U loop began with a marked bend at the junction and was abnormally directed. It was noteworthy, however, that cases in which the electrocardiograms did not show any U-wave abnormalities revealed such U-loop abnormalities just as markedly (Fig. 5).

Discussion

Since almost all of the subjects with left ventricular hypertrophy showed more or less of an abnormality of their T-U loop, this finding was quite useful for diagnostic purposes. In our cases there were many subjects who showed no (or minute) evidence of left ventricular hypertrophy in electrocardiographic deflections in spite of definite evidence of left ventricular enlargement in the chest roentgenograms. A study of the T-U loop in such cases revealed almost all of them to have some abnormality. Therefore, in the later stage of this study we could predict whether the subject was normal or not by examining the U loop first. To some extent we could also predict the presence of left ventricular hypertrophy. However, we cannot say whether or not such abnormality of the U loop is due to left ventricular hypertrophy. Some abnormalities of the U loop indicated old myocardial infarction or other cardiac diseases rather than left ventricular hypertrophy. Although the afore-mentioned abnormalities seemed to differ from the latter, we are not able to correlate specific configuration of the U loop with the various disease states as yet because of our limited experience.

That the actual U vector loop does not usually constitute a closed loop differs from our primary expectation, as well as that of Furbetta and his associates.[4] The reason for this is not completely clear. However, when the component electrocardiograms were examined at the high magnification of 1 mv. to 2.8 inches on the cathode-ray oscilloscope, the T-U segment was frequently not coincident with the base line. Even when it was on the base line in



SAGITTAL PLANE

GRADE \ CONFIGURATION	NORMAL	ABNORMAL: U LOOP ONLY			ABNORMAL: TU LOOP WITH T LOOP CONCORDANT TO QRS	ABNORMAL: TU LOOP WITH T LOOP DISCORDANT TO QRS
I	0	0	1	0	0	0
II	3	4	5	3	1	2
III	0	0	1	1	0	6

I: 1 case; II: 13 cases; III: 1 case;

FRONTAL PLANE

GRADE \ CONFIGURATION	NORMAL	ABNORMAL: U LOOP ONLY		ABNORMAL: TU LOOP WITH T LOOP CONCORDANT TO QRS			ABNORMAL: TU LOOP WITH T LOOP DISCORDANT TO QRS
I	0	0	1	0	0	0	0
II	6	1	3	5	1	2	0
III	0	0	3	0	1	2	1

I: 1 case; II: 12 cases; III: 6 cases;

HORIZONTAL PLANE

GRADE \ CONFIGURATION	NORMAL	ABNORMAL: U LOOP ONLY			ABNORMAL: TU LOOP WITH T LOOP CONCORDANT TO QRS		ABNORMAL: TU LOOP WITH T LOOP DISCORDANT TO QRS
I	0	0	0	1	0	0	0
II	4	6	2	2	0	1	2
III	0	0	0	2	1	0	5

I: 1 case; II: 12 cases; III: 3 cases;

Fig. *4*. Diagrams of the T-U vector loops of left ventricular hypertrophy. They were classified on the basis of configuration. Number of cases of each grade of left ventricular hypertrophy which showed such configuration is listed in this table. In the diagram of the vector loop, T loops are shown by broken lines, and U loops are shown by short solid lines with arrows on one end.

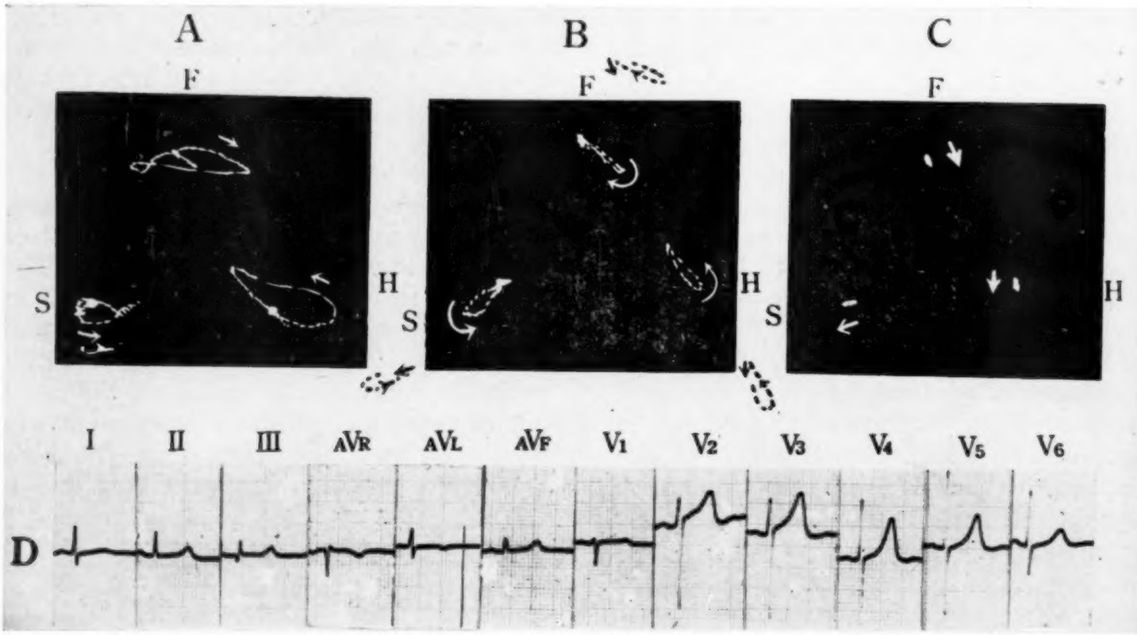


Fig. 5. An example of the T-U loop of left ventricular hypertrophy. A case of renal hypertension in a 54-year-old woman. Figure arrangements and abbreviations are the same as in Fig. 2. Major abnormality lies in the direction of the U loop. In this case the electrocardiogram is almost within normal limits, including the U-wave finding, as shown in *D*, in spite of the fact that the roentgenogram and physical examiation showed marked left ventricular enlargement, with systolic pressure of 178 and diastolic pressure of 98 mm. Hg. However, the U vector loop is definitely abnormal.

one component, it was usually not so in the other component perpendicular to this. When an electrocardiograph with a shorter time-constant is employed, the end of an actual upright T wave may be recorded more depressed, which may make an actually elevated T-U segment consistent with the base line.

Negative U waves of the electrocardiogram have been regarded by some authors as a more advanced sign than other electrocardiographic abnormalities. For example, Kemp and his associates[5] noticed that negative U waves were found in cases of more severe hypertensive heart diseases, and stated that in the evolution of the "left ventricular strain" pattern the inversion of the U wave is a late event that follows the inversion of the T wave by a certain time lag. They also observed that in the few cases in which an inverted U wave followed a positive T wave, morbidity and mortality were very high. Our clinical experiences were consistent with theirs to some extent. However, our present study suggested that the abnormality of the U vector loop developed long before the appearance of various other electrocardiographic abnormalities, including not only those of the U wave but also those of the T wave. Actually, abnormalities of the U loop alone appeared in cases of left ventricular hypertrophy of rather slight degree. Negative U waves in the electrocardiograms can be regarded as a terminal event in the evolution of the changes in the U vector loop. Therefore, it is natural that they have grave prognostic significance. On the other hand, abnormalities of the U loop alone can thus be employed to discover earlier stages of left ventricular hypertrophy.

Summary

1. U-loop vectorcardiograms were obtained from 30 normal subjects and from 31 subjects with left ventricular hypertrophy, by the method of differential vectorcardiography. Four of the subjects with left ventricular hypertrophy were excluded from the present study because of the complication of myocardial infarction.

2. The U loop of normal subjects showed a constant configuration. It re-

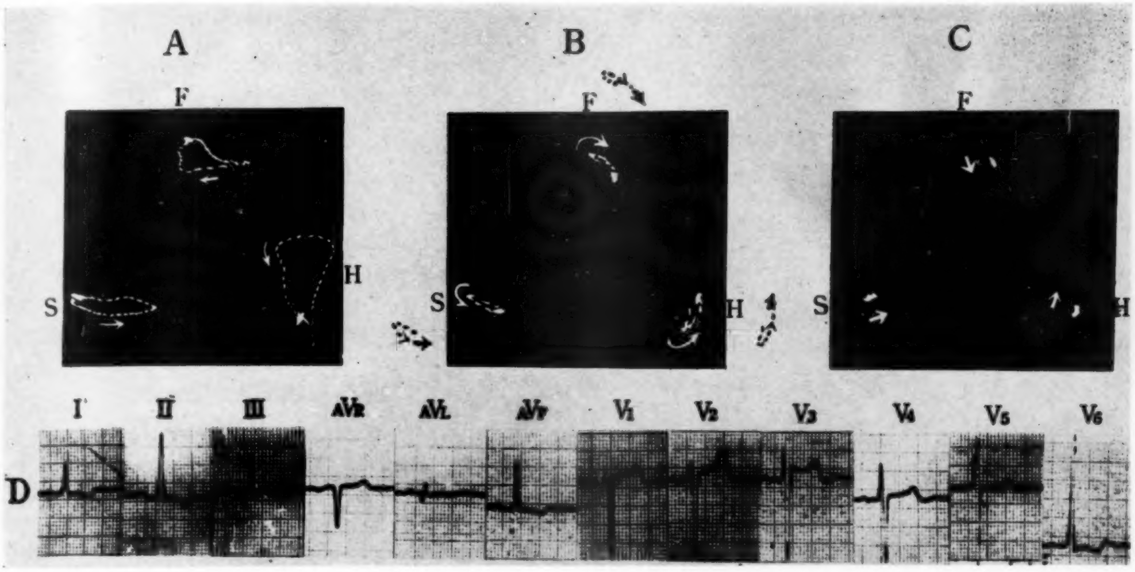


Fig. *6*. Another example of the T-U loop of left ventricular hypertrophy. A case of essential hypertension in a 67-year-old man. Figure arrangements and abbreviations are the same as in Fig. 2. The T loop is discordant with the QRS loop, and the U loop is also abnormal in its direction. The electrocardiogram showed marked left ventricular hypertrophy, with negative U waves in Lead V_6 and negative T-U segments in Leads V_3, V_4, and V_5. The roentgenogram and physical examination also revealed marked left ventricular enlargement.

sembled a small, slightly curved club and was inscribed almost in the direction of continuation of the terminal limb of the T loop, so that a term such as *U vector segment* or *U vector arc* might be preferable to the term *U vector loop*. The T-U junction vector was directed to the left, inferiorly, and mostly anteriorly. This finding of the U loop, together with that of the T loop, which was inscribed clockwise in the frontal plane and counterclockwise in the horizontal and left sagittal planes, with its long axis directed to the left, inferiorly, and slightly posteriorly or anteriorly, constituted characteristic features of the normal T-U loop.

3. The U loop of left ventricular hypertrophy began with a marked bend at the T-U junction and extended in various directions, resembling also a small curved club, but sometimes much larger than normal U loops. Occasionally, the U loop was inscribed as in normal cases, in continuation of the terminal limb of the T loop, but in such cases the T loop itself was abnormal. All cases of left ventricular hypertrophy showed such a feature of the T-U loop in at least one planar projection; there was one exception, however, a case in which normal features were retained in all three planes.

4. There was a tendency toward relatively slight left ventricular hypertrophy in those cases which retained normal features in any one of the planes or those which showed abnormality in the U loop only, whereas there was relatively marked left ventricular hypertrophy in those cases which showed a distinct abnormality also in the T loop.

5. Such U-loop abnormalities were already evident in the early stage of left ventricular hypertrophy when there were no (or minute) evidences of it in ordinary electrocardiograms, including the U-wave changes. Thus, they are useful for diagnostic purposes in detecting slight left ventricular hypertrophy.

The authors wish to express their appreciation to Mr. Hisashi Ohshima for technical assistance.

REFERENCES

1. Hellerstein, H. K., Shaw, D., and Sano, T.: Dissection of vectorcardiogram: differential vectorcardiography, Am. Heart J. **47**:887, 1954.
2. Sokolow, M., and Lyon, T. P.: Ventricular complex in left ventricular hypertrophy as obtained by unipolar precordial and limb leads, Am. Heart J. **37**:161, 1949.

3. Frank, E.: Accurate, clinically practical system for spatial vectorcardiography, Circulation **13**:737, 1956.
4. Furbetta, D., Bufalari, A., Santucci, F., and Solinas, P.: Abnormality of the U wave and of the T-U segment of the electrocardiogram. The syndrome of the papillary muscle, Circulation **14**:1129, 1956.
5. Kemp, R. L., Surawicz, B., Bettinger, J. C., Gottlieb, H., and Bellet, S.: Prognostic significance of negative U waves in the ECG in hypertension, Circulation **15**:98, 1957.

Case reports

Functionally corrected transposition of the great vessels without significant associated defects

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Within recent years, corrected transposition of the great vessels has been reported with ever-increasing frequency. Since Von Rokitansky[1] first discussed the anomaly in 1875, it has been reported and reviewed many times in the world literature. Harris and Farber[2] reviewed 17 cases in 1939, and presented a detailed discussion of some of the leading embryologic theories. Subsequent reviews by Cardell,[3] by Anderson and associates,[4] and most recently by Malers and associates[5] have begun to delve into the clinical and physiologic findings associated with this cardiac anomaly.

Corrected transposition is generally considered to exist when, in addition to the reversed anterior-posterior relationship of the aorta and pulmonary artery found in uncorrected transposition, there is associated mirror-image reversal. This mirror-image reversal can occur along the cardiac axis either at the level of the atrium, ventricle, or bulbus and is spoken of as "inversion." The distinction between inversion and transposition is made on an embryologic as well as a descriptive basis.[6] To qualify as corrected transposition this inversion must permit venous blood to enter the transposed pulmonary artery and then the lungs. The freshly oxygenated blood must then travel through its respective side of the inverted portion of the heart to the transposed aorta and thence to the systemic circuit. On the basis of this concept, several articles[2-7] have described the four possible types of inversion of the cardiac axis which converts transposition of the great vessels into "corrected transposition of the great vessels." These are: (1) bulbus inversion; (2) sinoatrial and ventricular inversion; (3) bulboventricular inversion; and (4) sinoatrial inversion. Malers[5] reported that 33 of 44 cases of corrected transposition for which anatomic types were recorded were of the bulboventricular type. Other authors[3,4,6] have concurred that this is probably the most common variety.

Fig. 1 illustrates the normal heart in comparison with transposition with bulboventricular inversion. As indicated in the bulboventricular type, the posteriorly placed pulmonary artery arises from a right-sided ventricle with the morphologic features of a normal left ventricle. The

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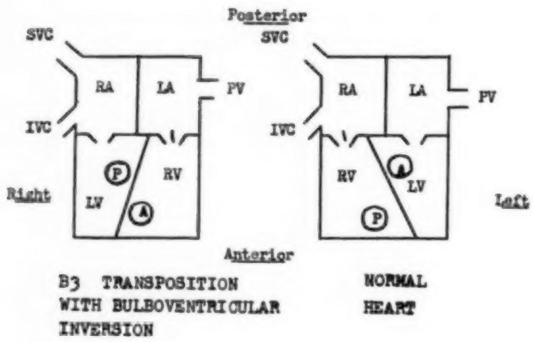

Fig. *1*. Diagrammatic illustration of the relationship of the various heart chambers and great vessels in the normal heart and in corrected transposition with bulboventricular inversion.

atrioventricular valve on this side resembles a normal mitral valve. The anomalously placed aorta, in turn, arises from the reversed type of situation.

Malers' further classification of "functionally totally corrected transposition" is useful and includes only those cases without associated shunts.[5] This means that the aorta now receives only fully oxygenated blood. In corrected transposition accompanied by a shunt, unsaturated blood may be delivered into the aorta, so that the transposition is not totally "functionally" corrected.

We present a case of "functionally totally corrected transposition of the great vessels," without any significant associated defects. These criteria have been met by only 6 of the 74 cases reviewed by Malers and associates,[5] and the diagnosis was elucidated by autopsy in each instance. Review of the literature failed to disclose a single case which had been correctly diagnosed clinically. Our patient has been closely followed up by his referring physician and has been clinically diagnosed at our Center. We present this report in the hopes that our findings, some of a different nature than previously reported, may shed additional light on the clinical and diagnostic features of corrected transposition by itself. Accordingly, it is our hope that these findings will aid others in uncovering an interesting cardiac abnormality which may be more common than was heretofore suspected.

Case report

This 11-year-old boy was first seen at the San Diego County Heart Center in December, 1959, for diagnostic studies. He was born of a normal pregnancy and labor, and growth and development have always been normal. Unconfirmed reports cited a murmur which was heard when he was 8 months old. He remained asymptomatic and was first seen by his referring cardiologist in March, 1953. At that time the findings were an accentuated second sound at the pulmonic area, with a Grade 2 (on the basis of 1-6) systolic murmur, best heard in the third intercostal space, along with a soft diastolic blowing murmur in the same area. X-ray films and fluoroscopic studies at this time revealed a globular heart shadow, marked fullness in the area of the pulmonary artery, and an unusual prominence of the left superior cardiac border.

The patient continued to remain asymptomatic; he did well in school and was able to participate in moderately active sports. In October, 1959, it was thought that the second sound in the second left intercostal space had become markedly accentuated. The latter was clinically interpreted as evidence to indicate increasing pulmonary hypertension, and catheterization was arranged. Review of the cardiorespiratory system gave entirely negative findings.

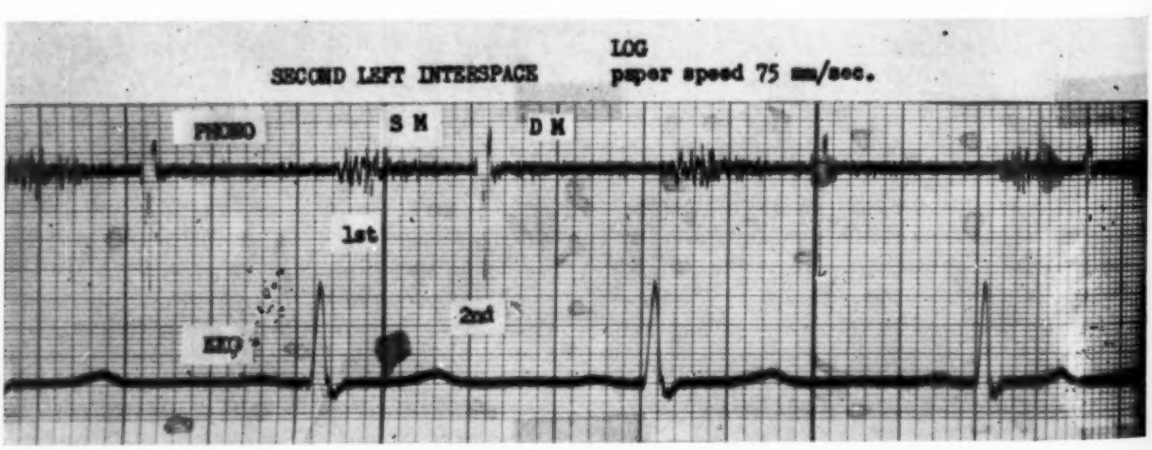

Fig. *2*. Phonocardiogram showing short systolic murmur, accentuated second sound, and decrescendo diastolic murmur.

Past medical history and family history were noncontributory.

Physical examination revealed an alert 11-year-old boy in no distress and without gross abnormalities. Cyanosis was not evident. The blood pressure was recorded in both upper extremities at 110/75 mm. Hg, with similar values in the right leg. The pulse was 84, and respirations were 16. The patient was in the sixtieth percentile for height, and the fortieth percentile for weight. Examination of the head and neck revealed no abnormal arterial or venous pulsations. The hepatojugular reflex was negative. Positive findings were confined to the cardiopulmonary system, where minimal left precordial asymmetry was noted. The chest was clear to percussion and to auscultation. The point of maximal impulse was located in the fifth intercostal space outside the mid-clavicular line, was forceful in nature, and suggestive of left ventricular enlargement. In addition, there was a definite lift to the lower portion of the sternum, such as one associates with right ventricular hypertrophy. A striking lift and closure tap were also noted in the second left intercostal space. Heart tones were audible at all valvular areas, and the second sound was markedly accentuated in the second left intercostal space, without detectable splitting. A Grade 2 systolic murmur was heard maximally in the second left intercostal space, and was transmitted to the apex and through to the back. Most noticeable in the second left intercostal space was a Grade 4 decrescendo diastolic blowing murmur immediately following the markedly accentuated second sound. The murmur was transmitted down along the left sternal border and could

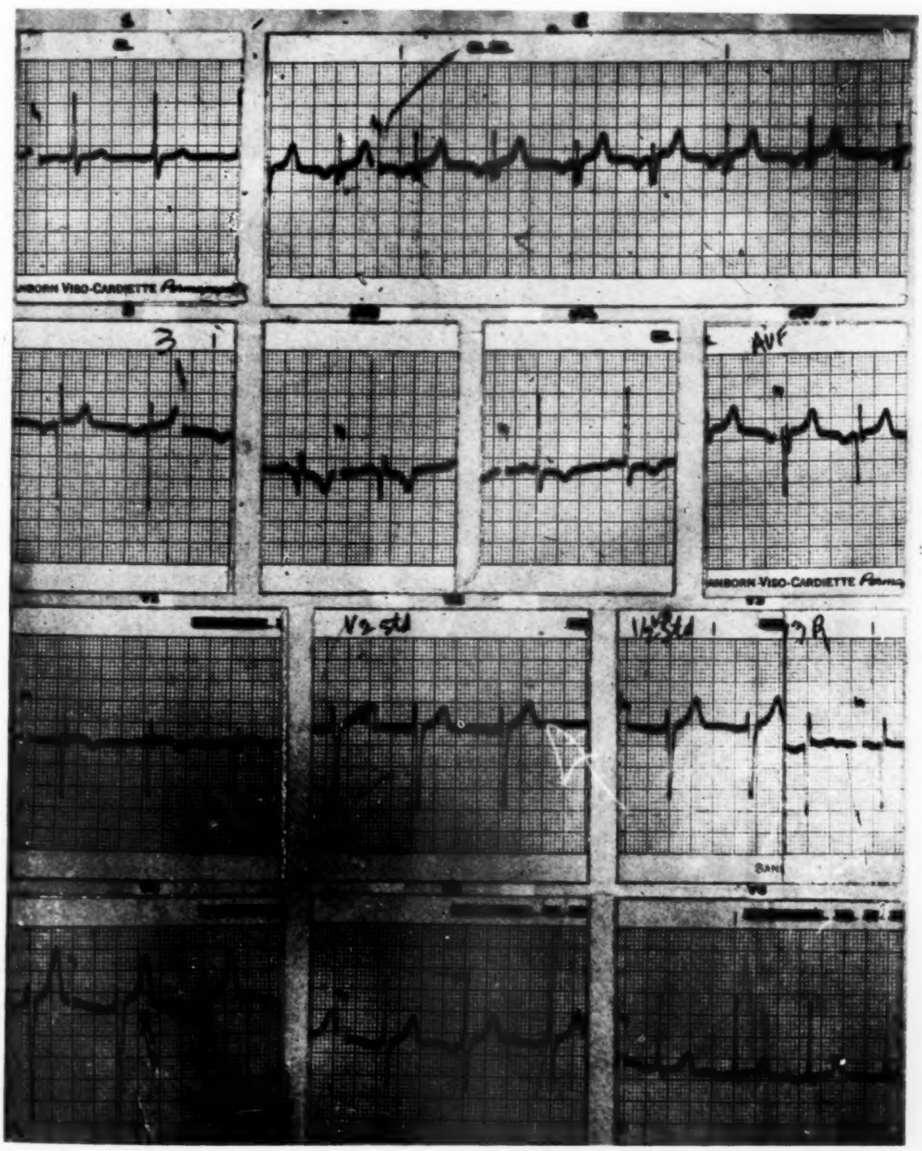

Fig. *3*. Routine 13-lead electrocardiogram with portions half-standardized. Note tall R waves in Leads I and aV_L, with abnormal R-T ratio in Lead aV_L, suggesting left ventricular hypertrophy.

Fig. *4*. Posterior-anterior view of chest with barium swallow. See text for description.

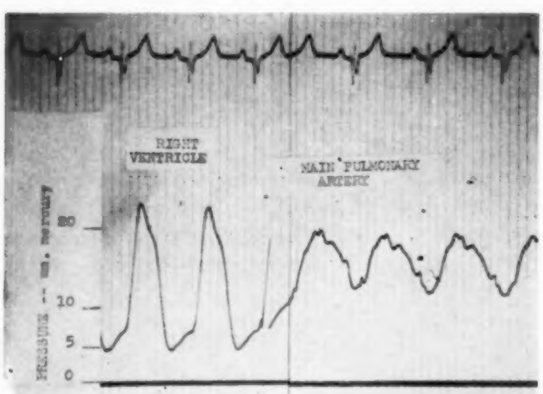

Fig. *5*. Pressure tracing from right ventricle and pulmonary artery. No insufficiency suggested.

be heard at the tricuspid area as well as at the left infraclavicular area. The peripheral pulses were regular and of normal quality, without any peripheral signs to suggest aortic insufficiency. The remainder of the physical examination as well as laboratory studies gave unremarkable findings.

A phonocardiogram (Fig. 2) substantiates the auscultatory findings. The electrocardiogram (Fig. 3) demonstrated a normal rate and rhythm. The P-R and QRS intervals were within normal limits. The findings showed definite left ventricular hypertrophy with associated "strain pattern" as noted in Lead aV_L. The R-R complexes in Leads V_{3R} and V_1 were attributed to rotational changes, and this was also reflected in Leads V_5 and V_6, as shown by the slurred S_{V6} with transition zone shifted to the left. A normal

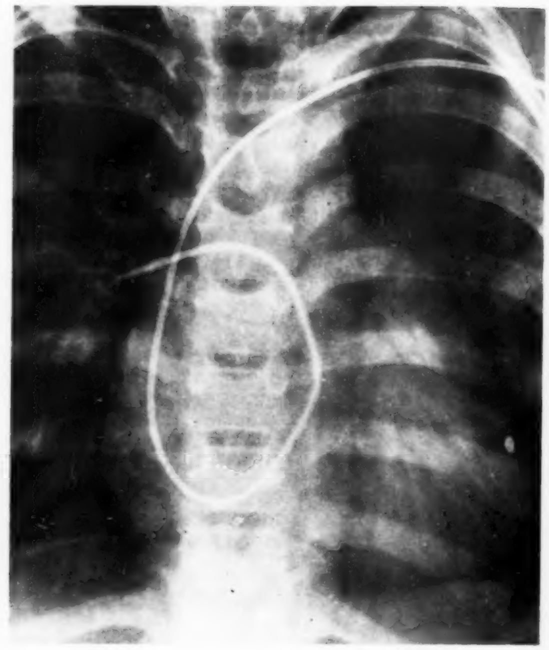

Fig. *6*. Posteroanterior projection. Spot film of catheter entering from left basilic vein and terminating in right pulmonary artery.

Fig. *7*. Lateral projection of catheter, as in Fig. 6.

progression of the R wave was present across the precordial leads. The P-wave inversion in Leads II, III, and aV_F was thought to represent a normal variant; however, the possibility of an ectopic supraventricular pacemaker could not be ruled out.

Fluoroscopy demonstrated a globular heart with a prominent, elongated, and convex left superior

Table I. Cardiac catheterization data

Location	*Pressure (mm. Hg) systolic/diastolic—mean*	*Oxygen (vol. %) (Van Slyke)*	*Oximetry (double scale)*
SVC	——	11.37	72.4
IVC	——	11.98	78.0
Right atrium	5/3 —5	11.22	71.0
Right ventricle	23/5 —11	11.61	72.3
MPA	19/12—5	11.67	72.3
Brachial artery	127/69—88	15.61 (94.2% sat.)	95.0

Cardiac index: 4.56 L./min./M.^{2}
Pulmonary index: 4.56 L./min./M.^{2}
Total pulmonary resistance: 223 dynes sec./cm.$^{-5}$
Total peripheral resistance: 1,308 dynes sec./cm.$^{-5}$

cardiac border. Forceful pulsations were seen most strikingly in the area normally occupied by the main pulmonary artery; however, this represented vigorous aortic pulsations. A posterior-anterior view of the chest (Fig. 4) showed a normal transverse cardiac diameter, and the medially placed pulmonary artery caused a characteristic notch on the barium-filled esophagus. The proximal indentation was that caused by the transverse portion of the aorta. Appropriate lateral views of the chest demonstrated minimal encroachment on the retrosternal space as well as some posterior displacement by the ventricular mass. Selective right or left ventricular enlargement could not be distinguished from the conventional films.

Catheterization and angiocardiography. Cardiac catheterization (see Table I) with angiocardiography was performed on Dec. 22, 1959. Pressures and samples from the entire right side of the heart and peripheral arteries were normal. Neither main pulmonary arterial, right ventricular, or brachial arterial pressure curves suggested insufficiency of either the pulmonic or aortic valves (Fig. 5). No intracardiac shunts were demonstrated. The abnormal path of the catheter was the only remarkable finding. A posteroanterior view (Fig. 6) showed the catheter entering an apparently normally placed right atrium, making a sharp bend over the spine, and exiting into the pulmonary artery through the medially placed location of the latter vessel. The lateral view (Fig. 7) showed the catheter again in the normal region of a right atrium, entering the right ventricle but then making a sharp-bend exit from a posteriorly placed pulmonary artery. Frontal and lateral angiocardiograms were obtained. Lateral views (Fig. 8*A*) showed the opacification of the right-sided atrium and ventricle in normal sequence. The right-sided ventricle showed a smoothness of the walls, with lack of a well-defined infundibulum and with a "tail-like" apex. The pulmonary artery was given off posteriorly. Opacification of the left-sided atrium and ventricle (Fig. 8*B*) were in normal sequence, with the endocardial surface appearing more trabeculated than the "right-sided ventricle." There was a

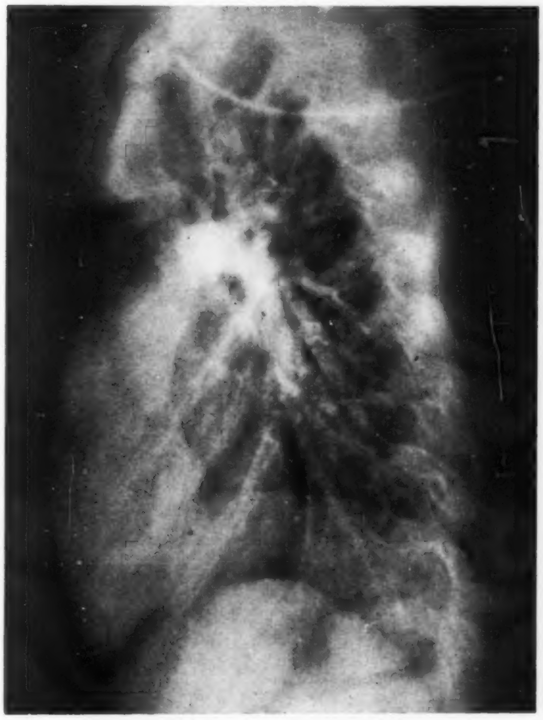

Fig. 8*A*. Lateral angiocardiogram with injection via cardiac catheter. Right-sided events. See text for discussion.

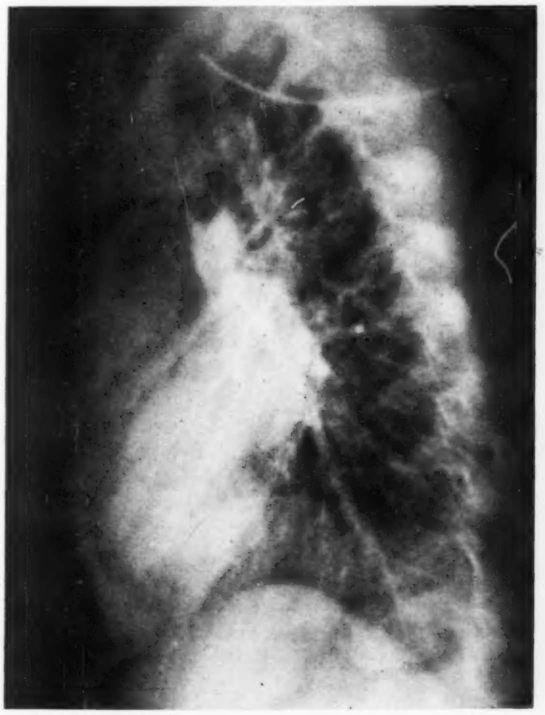

Fig. 8*B*. Lateral angiocardiogram, visualizing left heart and aorta.

Fig. *9A*. Frontal angiocardiogram, showing right heart and lesser circulation. See text for full description.

Fig. *9B*. Frontal angiocardiogram, illustrating left heart and aorta.

well-defined infundibulum at the outlet of the anteriorly placed aorta. Frontal views (Fig. *9A*) demonstrated a medially placed pulmonary artery. A later view (Fig. *9B*) showed the aorta arising from a left-sided ventricle in which a sharply demarcated infundibulum could be identified, as well as the abovementioned increased trabeculations. The angiocardiograms were thought to demonstrate "corrected transposition" of the great vessels with ventricular and bulbus inversion.

Discussion

The asymptomatic course of this 11-year-old boy demonstrates a possible reason for the paucity of reports of "functionally totally corrected transposition" without significant associated defects. The 6 cases reviewed by Malers[5] were diagnosed at autopsy; the ages of the patients ranged from 26 to 60 years, with indications that at least 2 out of the 6 died of noncardiac causes.[5,8]

We have attributed the diastolic murmur to probable pulmonic insufficiency, while keeping in mind the failure to demonstrate this at catheterization. The long-term clinical consequences of pulmonic insufficiency as noted in a recent article by Collins and associates[9] are not usually considered to be serious.

An electrocardiographic finding worthy of comment in our patient is the absence of atrioventricular block. Varying degrees of atrioventricular block was often noted as an important electrocardiographic diagnostic feature in most previous case reports describing corrected transposition.[3,4,5,7] The left ventricular "strain" pattern also merits comment in view of the speculation that this may well be associated with the fact that an anatomic right ventricle is handling the systemic load. It is also worthy of note that except for the physical signs of increasing pulmonary hypertension, which are probably due to the unique anatomic arrangement, this patient's condition might not have been diagnosed at this time. Suffice it to say, that angiocardiography accompanied by the anomalous route of the catheter on the right side of the heart are the final means of diagnosis.

We conclude this report with the observation that the heart is normally a well-designed and durable pump. It has in the case of this boy, by a unique variation which Nature seldom allows, recreated its arrangement to perform its total function adequately merely by substitution and rearrangement of parts. An anatomic right ventricle pumping at a systemic pressure leaves to pure speculation how long this patient's variation can continue to duplicate nature's normal arrangement.

Summary

The various clinical, electrocardiographic, radiologic, angiocardiographic, and cardiac catheterization features in a case of "functionally totally corrected transposition"

without any associated defects are presented. To our knowledge, this is the first case in which detailed studies are available and in which a diagnosis has been feasible ante mortem.

The authors wish to thank Dr. William C. Cooke for the privilege of studying his patient, and Mr. Harold W. Hartman for his aid in preparing the manuscript.

REFERENCES

1. Von Rokitansky, C. F.: Die Defekte der Scheidewande des Herzens, Vienna, 1875, W. Braumüller.
2. Harris, J. S., and Farber, S.: Transposition of the great cardiac vessels, with special reference to the phylogenetic theory of Spitzer, Arch. Path. **28**:427, 1939.
3. Cardell, B. S.: Corrected transposition of the great vessels, Brit. Heart J. **18**:186, 1956.
4. Anderson, R., Lillehei, C. W., and Lester, R. G.: Corrected transposition of the great vessels of the heart. A review of 17 cases, Pediatrics **20**:626, 1957.
5. Malers, E., Björk, V. O., Cullhed, I., and Lodin, H.: Transposition functionally totally corrected, associated with "mitral" insufficiency, Am. Heart J. **59**:816, 1960.
6. Kahn, M., Henry, E., Grazenas, N. V., and Steinfeld, L.: Atresia of the left atrioventricular valve associated with corrected transposition of the great vessels, Am. J. Med. **28**:1013, 1960.
7. Kjellberg, S., Mannheimer, E., Rudhe, V., and Jonsson, B.,: Diagnosis of congenital heart disease, Chicago, 1959, Year Book Publishers, Inc.
8. Schaeffer, J. A., and Rudolph, L. A.: Corrected transposition of great vessels, Am. Heart J. **54**:610, 1957.
9. Collins, N. P., Braunwald, E., and Morrow, A.: Isolated congenital pulmonic valvular regurgitation, Am. J. Med. **28**:159, 1960.

Large abscess of the heart and spleen complicating bacterial (enterococcal) endocarditis

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Myocardial abscesses are distinctly uncommon, and standard textbooks of cardiology fail to even mention them.[1] Nevertheless, they have been known to follow either hematogenous dissemination of bacteria from a distant focus or local extension from bacterial endocarditis.[2-11] They are said to be found in from 0.2 to 0.5 per cent of the total number of autopsies in a large institution.[5] For the most part, these abscesses are small, and recently we had the opportunity to see a case of multiple miliary abscesses of the interventricular septum due to an overwhelming staphylococcal (*Staphylococcus aureus*, bacteriophage type 80, 81) pneumonia. Similarly, in bacterial endocarditis, focal aggregations of phagocytes in the heart and various organs, with or without an associated nidus of necrosis, are a common finding,[1,7,12] but large myocardial abscesses are extremely rare.[6]

In the present communication we report the occurrence of a large myocardial and a huge splenic abscess complicating a fatal case of enterococcal endocarditis. The clinical and pathologic data are discussed with respect to the pathogenesis of the various manifestations of the disease.

Case report

The patient was a 52-year-old para IV, gravida 0 Puerto Rican woman who was admitted to Lincoln Hospital with the complaints of vomiting, generalized weakness, and epigastric pain that had been present for 3 days.

The patient admitted to consuming moderate amounts of alcohol over a period of many years, and in 1956, she underwent a subtotal gastrectomy and gastrojejunostomy at another hospital because of "an ulcer." At operation a liver biopsy was performed and was reported to show Laennec's cirrhosis. Since then she had been asymptomatic until 2 to 3 weeks prior to admission. At that time she first noticed generalized painless abdominal enlargement which tended to progress until the time of admission. In the 3 days prior to admission there had been repeated vomiting, weakness, swelling of both legs, anorexia, periodic sharp epigastric pain, and headache. As far as is known, there was no history of heart disease, rheumatic fever, shortness of breath, hemoptysis, chest pain, or recent hematemesis.

Physical examination at the time of admission revealed a well-developed Puerto Rican woman in no distress. The temperature was 99.0°F. rectally. Blood pressure was 130/80 mm. Hg. Pulse was 110 and regular. Respirations were 22. Several spider angiomata were seen on the chest. The sclerae were not icteric and did not show petechiae. The lungs were clear. Cardiac examination failed to reveal any murmurs or other abnormalities. The abdomen was protuberant and its surface showed engorged superficial veins and a healed midline surgical scar. The flanks were dull to percussion, and a fluid wave was elicited. The edge of the liver was palpable 5 fingerbreadths below the costal margin; its surface was firm and irregular. The spleen was not palpable. There was no peripheral edema.

At the time of the patient's admission the blood count showed a pancytopenia with a hemoglobin of 7.8 Gm. and a white blood cell count of 2,400.

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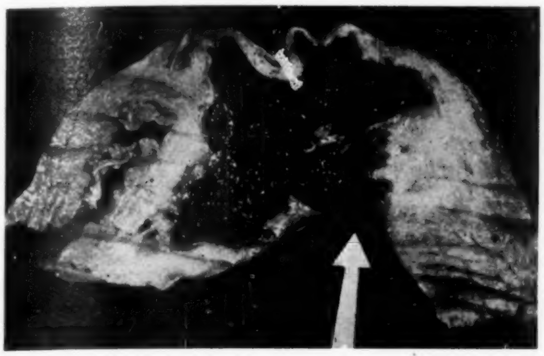

Fig. *1*. Cross section through the posterior wall of the left ventricle, showing the blood-filled myocardial abscess cavity, 2.5 cm. in diameter. The arrow points to the sinus tract connecting the abscess with the left ventricular chamber. Note that only a thin rim of myocardium separates the abscess from the pericardial space.

The differential count was normal. The liver profile indicated hepatocellular damage. The chest x-ray film revealed a normal cardiac silhouette and normal lung fields. The electrocardiogram was within normal limits.

Her protracted hospital course was stormy, complicated, and progressively downhill. Shortly after admission she became acutely ill, with a persistent fever of 100-104°F. A Grade 3 apical systolic murmur appeared, and left heart failure supervened. Gradual and progressive enlargement of the spleen occurred. She developed a small hematoma of the leg and several subconjunctival hemorrhages, pneumonia, focal seizures with left-sided symptoms, left hemiplegia, bilateral cortical dysrhythmia on the electroencephalogram, progressive anemia, positive stool guaiacs, pyuria and hematuria, mild azotemia, intermittent leukopenia and thrombocytopenia, and acute left upper quadrant pain. Serial cultures of blood and urine were positive for enterococci. She was treated with massive doses of penicillin and large doses of oxytetracycline, novobiocin, chloramphenicol, and streptomycin—alone and in combination—and she became afebrile during the last 6 weeks of her hospitalization. Clinically, though, she continued to deteriorate. Serial electrocardiograms showed only sinus tachycardia, and, terminally, multifocal ventricular premature contractions. On the one hundred and tenth day after admission the patient died.

Autopsy. The most striking findings on postmortem examination were in the heart and spleen.

The heart weighed 400 grams. The pericardium was unremarkable and the pericardial cavity contained only 20 c.c. of fluid. Grossly, the right atrium and tricuspid valve were normal. The right ventricular wall measured 1 cm. in thickness. The left atrium was approximately three times normal in size and its wall was thickened. The circumference of the mitral valve was slightly narrowed to 8 cm. The mitral leaflets were thickened and sclerosed, and their atrial surfaces were partially ulcerated and studded with small vegetations, 0.8 cm. in diameter. Microscopic sections of the leaflets revealed the changes of an old calcific rheumatic valvulitis with a superimposed acute inflammatory element; no bacteria were noted. The capacity of the left ventricular chamber was decreased. The papillary muscles of the left ventricle were hypertrophic and their chordae tendineae were shortened and thickened. The left ventricular wall was thickened to 2.3 cm. A clot of blood was attached to the undersurface of the posterior mitral leaflet, and was pocketed in the space bounded posteriorly by the posterior ventricular wall, superiorly by the posterior mitral leaflet, and anteriorly by the associated papillary muscles and chordae tendineae. Sectioning through this area showed that this blood clot was continuous via a sinus tract with a blood-filled abscess cavity contained within the posterior ventricular wall. This cavity measured 2.5 by 1.5 by 1 cm. Surrounding this large abscess cavity were several small satellite abscesses. Microscopic sections through the myocardium adjacent to the large abscess cavity showed extensive hyalinization and fibrosis, and calcified emboli within many of the small branches of the coronary arteries. The remainder of the left ventricle revealed foci of myolysis, fibrosis, hyalinization, and chronic inflammatory cells. Gram-staining of sections throughout the left ventricle frequently showed Gram-positive cocci (presumably enterococci) in the areas of bland necrosis. Grossly, the coronary arteries, aorta, pulmonary vessels, and semilunar valves were unremarkable.

The spleen weighed 900 grams. Grossly, half of the splenic surface had a grayish white color and was fluctuant. Sectioning of this area showed a large abscess cavity which measured 12 by 8 by 6 cm. and contained 260 c.c. of fluid pus and 280 grams of solid pus mixed with necrotic splenic pulp. Grossly, the remainder of the splenic parenchyma was normal. The hilar portion of the splenic artery was almost completely occluded by a calcified blood clot, and the vessel wall in this area showed acute endarteritis.

The lungs showed chronic passive congestion with multiple microscopic stasis infarcts. There was a right-sided pleural effusion of 250 c.c.

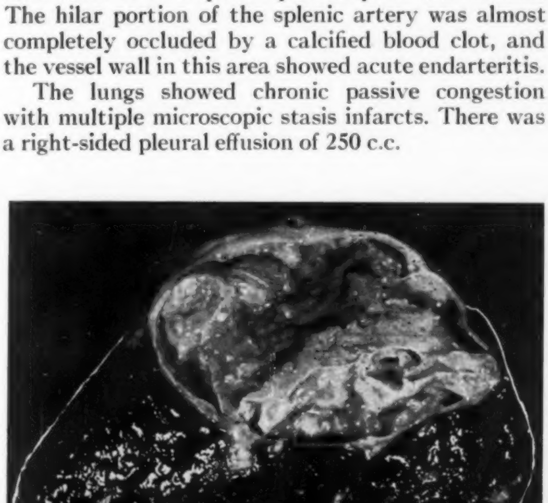

Fig. *2*. Cross section of the spleen, showing the huge splenic abscess, 12 cm. in diameter.

The liver weighed 1,600 grams and was the seat of Laennec's cirrhosis and chronic passive congestion. There was ectasia of the lower esophageal venous plexus but there was no ascites.

The surfaces and cut sections of both kidneys were speckled with numerous serous cysts which measured 0.4 to 4.0 cm. in diameter. On microscopic study, one of the tiny branches of the renal artery was seen to be occluded by a calcified embolus. The glomeruli showed extensive changes consistent with the focal glomerulonephritis of Löhlein-Barhr. Also noted was a chronic interstitial infiltrate suggestive of pyelonephritis.

The pancreas showed microscopic bands of fibrosis with chronic inflammatory cells.

The cerebral vessels, meninges, and brain were normal grossly, except for some softening of the right lenticular nucleus and internal capsule. Microscopic study showed minute foci of acute infarction and liquefaction necrosis scattered throughout the cerebral cortex.

Final diagnoses. (1) Rheumatic heart disease, mitral stenosis and insufficiency, biventricular hypertrophy, left atrial dilatation and hypertrophy, normal sinus rhythm, compensated at the time of admission. (2) Enterococcal bacterial endocarditis of the mitral valve superimposed on diagnosis No. 1. (3) Enterococcal septicemia due to diagnosis No. 2. (4) Large abscess of the heart (left ventricle) due to diagnosis No. 3. (5) Large abscess of the spleen due to diagnosis No. 3. (6) Enterococcal myocarditis due to diagnosis No. 3. (7) Emboli to the heart, brain, spleen, and kidneys due to diagnosis No. 2. (8) Chronic alcoholism. (9) Laennec's cirrhosis due to diagnosis No. 8. (10) Esophageal varices with bleeding due to diagnosis No. 9. (11) Splenic endarteritis due to diagnosis No. 7. (12) Focal glomerulonephritis due to diagnosis No. 2. (13) Chronic pyelonephritis. (14) Chronic interstitial pancreatitis due to diagnosis No. 8. (15) Status post old subtotal gastrectomy and gastroenterostomy for peptic ulcer.

Discussion

It is worthy of note that the subacute bacterial endocarditis was engrafted on a rheumatic mitral valvulitis showing only a mild degree of valvular deformity, so mild in fact that on admission the patient was asymptomatic, a murmur was not detectable, and the electrocardiogram and cardiac silhouette were within normal limits. The normal circumference of the mitral ring is approximately 10 cm.,[7] but, as a rule, symptoms of mitral stenosis do not appear until the circumference contracts below 4 or 5 cm.[13]; in the case described the mitral circumference was 8 cm.

A striking feature of the case was the absence of fever and leukocytosis in the latter part of the patient's course, despite the presence of a huge splenic abscess, a smaller myocardial abscess, and dissemination of the organism throughout the body. Perhaps this can be attributed to sterilization of the blood by antibiotics, since the blood cultures became negative in the latter half of her hospitalization.

The case described provides several clues to the pathogenesis of the initial bacteremia responsible for the bacterial endocarditis, and for the subsequent formation of the myocardial abscess and congestive heart failure. It has been suggested that enterococcal bacteremia can result from acute functional gastrointestinal disturbances,[1] and just such a picture antedated the patient's hospitalization. Alcoholism, or perhaps an intercurrent viral infection, may have been responsible for the gastroenteritis.

The formation of a myocardial abscess may result from (a) contiguous extension of septic valvulitis into the myocardium, (b) hematogenous dissemination of septic emboli through the coronary arteries, or (c) bacterial myocarditis secondary to a generalized sepsis. In the present case there is pathologic evidence that the latter two routes were responsible for the abscess.

The causes of the congestive heart failure in this case are clearly evident: (a) the precipitation of progressive mitral insufficiency by the bacterial endocarditis, (b) multiple coronary emboli, (c) diffuse interstitial enterococcal myocarditis, and (d) destruction of myocardial tissue by the abscess. Contributory factors would include (e) the "toxicity" of infection, and perhaps (f) prolonged sinus tachycardia.

The heart failure, however, was reasonably well controlled and was not, in itself, responsible for the death of the patient. The immediate cause of death remains conjectural, and one can only suspect that the abscess, being an "irritative focus," resulted in an ectopic rhythm and an electrical death. Thus, the ventricular premature contractions noted in her last electrocardiogram may have been an ominous forecast of things to come.

Summary

A case is described of enterococcal endocarditis superimposed on an unsuspected and asymptomatic rheumatic valvulitis. The clinical course was progressively downhill despite intensive multiple antibiotic

therapy. The picture included all of the usual sequelae of uncontrolled subacute bacterial endocarditis, including septic emboli to several organs and vessels, appearance of the murmur of mitral insufficiency, diffuse focal glomerulonephritis, etc. The unusual feature, however, was the postmortem finding of a large myocardial abscess, 2.5 cm. in greatest diameter, and a huge splenic abscess, 12 cm. in greatest diameter.

REFERENCES

1. Friedberg, C. K.: Diseases of the heart, ed. 2 Philadelphia, 1956, W. B. Saunders Co.
2. Weiss, S., and Wilkins, R. W.: Myocardial abscess with perforation of the heart, Am. J. M. Sc. **194**:199, 1937.
3. Zettner, A., and Irmiere, V. J.: Abscess of the heart: a complication of acute vegetative and ulcerative endocarditis, Circulation **20**:590, 1959.
4. Tennant, R., and Parks, H. W.: Myocardial abscess: a study of pathogenesis, with a report of a case, A.M.A. Arch. Path. **68**:456, 1959.
5. Flaxman, N.: Myocardial abscess, J.A.M.A. **122**:804, 1943.
6. Berger, A. R., and Kossmann, C. E.: Solitary myocardial abscess in subacute bacterial endocarditis, Ann. Int. Med. **35**:1125, 1951.
7. Gould, S. E.: Pathology of the heart, ed. 2, Springfield, Ill., 1960, Charles C Thomas.
8. Sheldon, W. H., and Golden, A.: Abscess of the valve ring of the heart; a frequent but not well-recognized complication of acute bacterial endocarditis, Circulation **4**:1, 1951.
9. Tedeschi, C. G., Stevenson, T. D., Jr., and Levenson, H. M.: Abscess formation in acute myocardial infarction, New England J. Med. **243**:1024, 1950.
10. Saphir, O.: Myocarditis: a general review with an analysis of 240 cases, Arch. Path. **32**:1000, 1947.
11. Abraham, E., and Jackson, M. M.: Rupture of the aortic valve and abscess of the valve ring complicating bacterial endocarditis, Am. Pract. & Digest Treat. **3**:781, 1952.
12. Libman, E., and Friedberg, C. K.: Subacute bacterial endocarditis, ed. 2, New York, 1948, Oxford University Press.
13. Dexter, L.: Pathologic physiology of mitral stenosis and its surgical implications, Bull. New York Acad. Med. **28**:90, 1952.

Review

The nephrotic syndrome

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This common but extraordinary condition is known by many names. By older pathologists it was referred to as *chronic parenchymatous nephritis* or the *large white kidney*. In 1913, Munk,[110] noting anisotropic fat in the urine of some patients with florid syphilis, called it *lipoid nephrosis*, a name which soon received the endorsement of Volhard and Fahr's famous classification of renal disease. More recently, Ellis' term *Type II nephritis* has been widely used,[38] but the electron microscope has revealed more subtle differences. The terms *lipoid or genuine nephrosis* and *membranous glomerulonephritis*[12] have been used interchangeably to describe the thickening of the glomerular basement membrane so commonly seen even by light microscopy, but some[79] would separate even these two conditions, applying the former term only to those kidneys in which the sole lesion is in the glomerular epithelial cells known as podocytes.

The view is here taken that the noun *nephrosis* should be abandoned in favor of the term *nephrotic syndrome*, which is applied in a loose descriptive sense to all patients with proteinuria, hypoalbuminemia, hyperlipemia, and edema, without regard to the renal lesion, although variations are common. Since all such patients thus far appropriately examined have shown changes in some part of the glomerular filter, and since progressive thickening of this membrane so often leads to glomerular hyalinization, the term *membranous glomerulosclerosis* appears to be a reasonably satisfactory way of grouping together the various etiological entities. The nephrotic syndrome thus becomes a constellation of clinical abnormalities which may have many "causes." It should be regarded in the same light as such other phenomena as fever, jaundice, anemia, cyanosis, etc. For those reluctant to give up established terms the idiopathic variety of this sclerosing lesion is synonymous with *lipoid nephrosis*. Until much more is known about the chemistry of renal protoplasm it seems premature to separate "podocyte disease" from processes involving the basement membrane also. Even the electron microscopists disagree; some emphasize the primacy of the epithelial (podocyte) lesions,[40,44] whereas Spiro[147] describes gaps in the basement membrane through which epithelium and endothelium come in contact, and Movat and McGregor[106] claim that the basement membrane only appears to be thickened because of a layer of extravasated protein beside it. A number of observations suggest that the most common lesion in any disease accompanied by the nephrotic syndrome is swelling and smudging of the foot processes of the epithelial layer of Bowman's membrane, and that this change may be reversed by steroid therapy.[44] Thickening of the basement membrane and other glomerular lesions are apparently permanent.

Clinical features. The patient, usually young, swells insidiously and to a degree

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which varies from a trace of puffiness about the face and ankles to the most grotesque dropsy. There is usually nothing in the history to explain the illness, although many give a vague account of "allergy" of one kind or another.[95] Subjective complaints are few, except for a sense of heaviness. The arterial blood pressure is usually normal. Pallor is often striking, but anemia is seldom marked unless the patient is also uremic. Muerhcke[109] has described parallel white lines in the fingernails which he thinks are indicative of hypoalbuminemia, but we have seen them infrequently. Intercurrent infections are frequent; the respiratory tract and the peritoneum are especially vulnerable to hemolytic streptococci and pneumococci, and these infections are often accompanied by bacteremia which may not be transient. This susceptibility to infection may be related to the low gamma-globulin content of the serum and to consequent lack of antibody formation. Spontaneous remissions occur,[138] sometimes during convalescence from such contagious diseases as measles or chicken pox, but relapses are common. In such patients the appetite is poor and a very large loss of tissue mass may be masked by the edematous fluid. If the renal lesion does not heal, the kidney eventually shrinks, the blood pressure rises, and symptoms associated with the uremic syndrome appear. It is commonly said that the nephrotic syndrome disappears as renal failure advances because contracted kidneys excrete less protein, but most patients with hypertension and uremia due to disease of the basement membrane remain somewhat edematous to the end, partly no doubt because of heart failure and anemia. A few, however, never have edema at any stage of the disease, and in them the diagnosis can only be suspected from the magnitude of the proteinuria and the presence of oval fat bodies in the urine. There is no evidence that these so-called "dry nephrotics" have a better prognosis than do those with edema.

Pathogenesis

Edema. From the patient's viewpoint, dropsy is the most conspicuous feature of this fascinating disorder, but it is important to note that profound disturbances in the metabolism of protein, fat, and electrolytes also occur. Although it is an extraordinary thing that an organism should find it necessary to enlarge itself with brine, the physician who limits his therapy to measures designed solely to increase the flow of urine is taking much too small a view of the problem. Indeed it is probable that the retention of salt water may even serve a useful purpose.* The circulation may be unable to meet the metabolic needs of the body, either because the cardiac output is too low or because the blood volume is too small. The renal tubule responds to these stimuli by resorbing sodium and water at an accelerated rate. The cardiac output is normal in patients with the nephrotic syndrome unless heart failure coexists or blood volume shrinks greatly, but the best measurements indicate that hypovolemia, perhaps only in some critical part of the vascular tree, is a common and possibly an essential feature.[22] Hypoproteinemia from any cause lowers oncotic pressure.[6] The chief force which holds water inside the capillary bed is the osmotic pressure of plasma proteins; when this is reduced, water tends to move to an extravascular position and blood volume falls. If protein depletion continues, this shrinkage may lead to critical drops in blood pressure and flow, which in turn produce antinaturiesis and antidiuresis by reflex mechanisms integrated in the hypothalamus.† There is evidence that secretion of aldosterone is controlled by a "glomerulotrophic" hormone from the posterior diencephalon.[42] Saline is returned to the body by the renal tubules in an effort to counterbalance the falling blood volume, but since plasma oncotic pressure is low because of hypoproteinemia, the fluid cannot stay within the capillary bed and passes outward to interstitial spaces. Bioassay suggests that the formation of both aldosterone and ADH are increased as integral parts of the neph-

*Leutscher[122] says, "I have repeatedly emphasized that the patient with the nephrotic syndrome must dilute his plasma in order to stay alive. If he tried to maintain a normal plasma colloid osmotic pressure with his greatly reduced quantity of circulating protein, his plasma volume would be so small as to make life impossible. A similar situation may exist in hepatic cirrhosis, complicated by diversion of fluid into the peritoneal cavity. If we exchange blood flow for blood volume cardiac failure might be included."

†It is admittedly difficult to understand why patients with idiopathic analbuminemia have minimal edema.[96]

rotic syndrome,[95] but there are many patients—the so-called *dry nephrotics*—whose hypovolemia is presumably too slight to produce edema. Even though it is always pleasant to watch a nephrotic patient diurese, the physician must constantly fix his attention upon that metabolic dysfunction which is more important than edema and probably the most fundamental cause thereof—hypoproteinemia.

Hypoproteinemia. The depletion of protein which is so characteristic of the nephrotic syndrome can be due to (a) diminished formation, (b) increased excretion, (c) increased destruction, or (d) any combination of these three possibilities. There are no good reasons for believing that synthesis of plasma proteins is defective; on the contrary, hypoproteinemia is a potent stimulus to this process. Available studies indicate that the formation of protein is at least normal.[19] Most patients are eating well when the syndrome appears, and few have any demonstrable liver disease. There is, on the other hand, no doubt that chronic proteinuria makes demands upon stores of protein which may not be met indefinitely. Squire[150,151] believes that external loss is the chief reason for the hypoproteinemia, but it is often difficult to detect any consistent correlation between the amount of protein in the urine and the lack of it in the serum. It is difficult to resist the idea that increased protein catabolism may be an important factor. The volume of glomerular filtrate is so large (approximately 180 liters per day) and the concentration of albumin so appreciable (150 mg. per liter) that a considerable amount of albumin (27 Gm.) must of necessity be resorbed by the tubules. In addition, a large quantity of nonprotein nitrogen is also filtered and resorbed and is thus available for metabolic purposes. Even slight defects in the tubular transport mechanisms may thus in time account for very large deficits of protein. If, for example, none of the filtered albumin were returned to the blood stream as such, the daily deficit would be about 30 Gm., a much larger amount than that usually lost in the urine by the nephrotic patient, and a close approximation to the 0.25 Gm. of serum albumin per kilogram of body weight formed daily by the normal adult.[149] One might expect to find that renal venous blood contains less serum albumin and more nonprotein nitrogen than does other venous blood, in comparison with simultaneous arterial analyses, and several groups have found this to be the case.[37] Conflicting evidence acquired by perfusing rat kidney with I^{131}-albumin exists, however.[144] In addition, Harms[65] has shown that these arteriovenous differences are accentuated in rats with antikidney serum nephritis, and he has furthermore shown that the proteolytic activity of such kidneys is definitely greater than normal. Gitlin and colleagues[60,61] and Kaitz[78] reported that radioactive protein given intravenously disappeared from the blood stream of nephrotic patients much more rapidly than from the circulation of normal subjects. Freeman and Mathews[53] reported that the nephrotic patient differs from the normal person in that albumin catabolism is increased as a fraction of the intravascular pool but decreased as grams per day. Conflicting data on patients with idiopathic hypoalbuminemia suggest either that protein is catabolized somewhere at an excessive rate or that it is lost in the stools.[3,126,142,153] I^{131}-labeled albumin disappeared from the blood stream of mice much more slowly if both ureters were ligated or both kidneys removed.[123] Although Chinard's calculations indicate that proteinuria is due to glomerular disease,[28] decreased tubular resorption may also be a factor,[52,135] and the beneficial effects of adrenocortical steroids in the nephrotic syndrome may be attributed not only to their action upon capillary permeability but to a possible normalizing effect upon the tubular transportation of nitrogenous compounds.[64]

Lipemia. Although a rough inverse relationship exists between the serum concentrations of albumin and fat in the nephrotic syndrome, there are nonrenal diseases (cirrhosis of the liver, starvation, for example) in which no such correlation exists.[73] The metabolism of lipoproteins is a new and difficult field, but several generalizations of clinical importance have emerged from accumulated evidence.[104,124a]

A. Lipids become water-soluble only when linked with plasma proteins. About two thirds of the total plasma lipid is normally contained in the beta-lipoprotein

fraction; the alpha-globulins carry the remainder. In the nephrotic syndrome all lipid fractions are increased, neutral fat most of all, and cholesterol more than the triglycerides and the phospholipids. Lactescence of nephrotic serum is determined by the relative amount of low-density (Sf 10-200) lipoprotein molecules; patients with the least amount of circulating albumin and the most edema are apt to have the creamiest sera. Those with milder varieties of the condition who have clear serum have hyper-beta-lipoproteinemia, with high-density (Sf 3-9) molecules predominating.

B. In normal subjects, lipoprotein synthesis seems to begin in the low-density range, the molecules of which convert to the high-density type with the transfer of lipid to albumin molecules. In the nephrotic syndrome this conversion is inhibited for unknown reasons, so that Sf 10-200 complexes accumulate. Conversion is facilitated (and lipemia combated) by infusions of albumin or by transplantation of the ureters of nephrotic animals to their own great veins to prevent loss of albumin.[133] Numerous studies indicate that the turnover rates of lipids and lipoproteins are prolonged in nephrotic animals and man.[8,10,59] Consistent abnormalities in lipoprotein-lipase activity have not been demonstrated. The role of the "lipid-mobilizing factor" has not yet been clearly established,[148] but heparin has marked ability to remove the Sf 10-200 molecules very rapidly from the serum of some nephrotic patients. The accumulation of lipids in serum has been likened to a "traffic jam" occasioned by the circumstance that, by one means or another, protein is disposed of more rapidly than is fat.

Increased permeability of Bowman's membrane leads to disproportionate loss from the serum of the smaller protein molecules (albumin, alpha-globulin ceruloplasmin, transferrin, etc.). Predominance of the larger complexes results (alpha 2-globulin, beta-globulin, fibrinogen).[88]

Other laboratory abnormalities. The mystery of the nephrotic syndrome lies in the fact that the urine contains too much protein, the serum too little. If electrophoretic patterns of the two fluids are compared, one is seen to be the rough inverse image of the other, particularly in regard to the albumin contained in each. There is a vague positive correlation between the intensity of the proteinuria and the severity of the hypoproteinemia, but patients who excrete 30 Gm. of protein daily (mostly albumin) often have a concentration of serum albumin no lower than that of those who have much lower excretion rates of albumin. Proteinuria greater than 3.5 mg. per day is rare in other diseases.[15] The concentration of serum albumin is commonly reduced to about 1.0 Gm. per cent, but virtual analbuminemia has been seen. Serum cholesterol may be in excess of 1.0 Gm. per cent.

The blood count is normal in the early stages, although the hematocrit may be a little high because of hypovolemia. When renal insufficiency appears, a normochronic and normocytic anemia is usually found, due possibly to erythropoietin deficiency. Hypoferremia and hypocupremia have been reported,[26] probably because metal-binding proteins are lost in the urine. The serum PBI is also often low because of the inability of plasma proteins to bind normal amounts of organic iodine,[128,132] but the rate of uptake of radioiodine is normal. Despite a low basal metabolic rate there is no evidence of hypothyroidism. The thyroid responds normally to TSH and desiccated thyroid. The titer of antistreptolysin-O in the serum is usually low, in contrast to the increase so commonly seen in proliferative glomerulonephritis; circulating complement is also reduced.[95]

Gross hematuria is rare, but showers of red cells may appear in the urine from time to time. Leukocytes, epithelial cells, and casts are surprisingly scanty. The important diagnostic clues are: (1) the presence of *oval fat bodies*, large epithelial cells full of fat droplets which are stainable with Sudan III, or which can be seen with polarized light as doubly refractile Maltese crosses, and (2) heavy proteinuria, an amount in excess of 3.5 Gm. per day being highly suggestive.[15] Urinary protein is chiefly albumin, chemically and immunologically identical with normal serum albumin. Heavy globulinuria has been regarded as a bad prognostic sign,[18,71] but this has been denied by others.[25]

Renal function. The nephrotic syndrome often appears in patients whose renal func-

tion is entirely normal even when tested by refined clearance and saturation techniques[9,24,102]; indeed, many have abnormally high rates of renal blood flow and glomerular filtration.[23] Later, reduction of these values bespeaks glomerular fibrosis, arteriolosclerosis, or infection. Tubular dysfunction is evident in many ways. Occasional patients excrete small amount of glucose and/or amino acids.[74,145,157] Since many nephrotic subjects have relatively normal glomerular filtration rates and serum electrolyte concentrations, it is certain that their edema is of tubular origin. The mere presence of edema is *prima facia* evidence that the kidney is excreting less sodium than the blood brings to it, and the fact that the serum is often hyponatremic is evidence that water is retained more tenaciously than salt. Conceivably, the proximal convolution can resorb isotonic fluid at an increased rate, but there is no evidence that this occurs as an isolated phenomenon. Little is known about the impact of disease upon the concentrating and diluting mechanisms of the loop of Henle, but the forces making for countercurrent diffusion may in some obscure way become so distorted as to intensify the resorption of water by the collecting ducts. Efforts have been made to find a common basis for the disturbances in renal handling of protein, salt, and water. It has been suggested, e.g., that the increased rate of protein catabolism liberates potassium which the kidney must excrete, and that retention of sodium occurs in a compensatory manner, but the losses of nitrogen and potassium are not always proportional.[103] Abnormal permeability of cell membranes to the transfer of Na^+, K^+, and protein may be of adrenocortical origin.[134] Metcoff et al.[101] showed that the nephrotic kidney responds to Diamox and to a nonresorbable anion (PAH) by excreting far more K^+ than does the normal kidney, possibly because of intense concentration of sodium; they also showed that the nephrotic kidney can secrete hydrogen even under the influence of carbonic-acid inhibitors, whereas the normal kidney cannot.

The nature of the renal lesion

For many years internists have regarded patients with the nephrotic syndrome as atypical examples of glomerulonephritis despite the fact that hematuria, hypertension, and unequivocal evidence of antecedent streptococcal infection are often conspicuously absent. It was assumed, therefore, that the initial episode had been overlooked or forgotten, but pediatricians have long been inclined to believe that the two disorders are unrelated,[8] the strongest arguments being that the nephrotic syndrome often appears in children who, on an average, are distinctly younger than those in whom acute hemorrhagic nephritis of the post-streptococcal variety usually occurs, and that serological evidence of bacterial infection is seldom found in the nephrotic syndrome. Longcope[92] pointed out that the clinical course in patients suffering from acute hemorrhagic glomerulonephritis (Type A) differs in many respects from that seen in patients suffering from the nephrotic syndrome (Type B), and later Ellis[38] renamed these groups Types I and II. Clinicians are now generally inclined to the view that the renal response to infection with certain strains of beta-hemolytic streptococci carries a relatively good prognosis, but that most patients whose illness begins with the nephrotic syndrome die of renal failure. Experimental evidence, however, suggests that the same agent may, under different circumstances, cause either epithelial proliferation or simple thickening of the basement membrane. Mixed lesions are commonly found in human kidneys. The view is here taken that certain strains of beta-hemolytic streptococci are only one of many different agents capable, under appropriate conditions, of causing the membranous changes so characteristic of the nephrotic syndrome. Glomerulosclerosis then is due to many factors but is all too often idiopathic (for this group, *genuine* or lipoid *nephrosis* are the conventional names but, in our opinion, less satisfactory ones). A considerable proportion of patients give a history which suggests hypersensitivity reactions.[95] Bacteria other than streptococci have evoked the disease, and it is possible that viruses may do so also.

Bell[12] was evidently the first to apply the term *membranous glomerulonephritis* to this lesion, but he expressed uncertainty as to whether it was related to antecedent

streptococcal infection or not. In splendid reviews, both Allen[4] and Ehrich[35] have accepted this dual concept and emphasized its importance. In early stages the glomerular capillaries are widely patent and there is none of the endothelial proliferation and intracapillary thrombosis so characteristic of post-streptococcal disease; later, when hyalinization and fibrosis have destroyed all glomerular landmarks, it may be impossible to distinguish between the two varieties. Some kidneys show both sclerotic and exudative changes. If hypertension has existed for any length of time, arterial and arteriolar sclerosis are found, and necrotizing vasculitis suggests the clinical picture of malignant hypertension. The tubular changes, once thought to be of primary importance, are now regarded merely as visible evidence of the fact that the glomerular filtrate contains more fat and protein than the tubules can comfortably deal with. The proximal convolutions especially, and, to a lesser degree, the straight segments and the distal convolutions, contain such large quantities of lipoprotein in droplet form that the epithelial cells themselves are often swollen and flattened; the droplets stain with Sudan III, and the esterified cholesterol in them reveals itself under polarized light as the well-known but infrequently searched for doubly refractile lipoid bodies. The collecting tubules are not often involved. Hyaline, granular, and fatty casts lie in the tubule lumens. The whole kidney may have a soft, yellowish, greasy look, but in later stages atrophy of some nephrons, hypertrophy of others, and overgrowth of connective tissue make for a small, rough organ. As the number of functioning nephrons diminishes, the amount of protein and formed elements in the urine naturally decrease also. Gross hematuria is apt to result from arteriolar necrosis.

A small proportion of nephrotic subjects shows no glomerular lesions in tissue sections examined by light microscopy, but the electron microscope demonstrates changes in the glomerular basement membrane and especially in the podocytes.[41,44,106,147] The earliest and apparently the most specific lesion consists of a swelling of the epithelial cells of Bowman's capsule and of coalescence of their foot processes; this seems to antedate the proteinuria and somehow to be responsible for it. The lesion is a reversible one which disappears during clinical remissions.[46] The splitting and thickening of the basement membrane so regularly seen regardless of etiology is likely to be permanent and to progress to complete glomerular hyalinization. Hence, the term *glomerulosclerosis* seems apt. It should be pointed out, however, that the tubular epithelial cells and the podocytes are embryologically identical, and that both rest upon a common basement membrane; disease in the glomeruli, therefore, bespeaks disease in the convoluted tubules, and leakage of protein into the urine may correlate with disordered tubular transport of protein. No pathognomonic tubular lesions have been described but they may be obscured by the masses of lipoprotein droplets which so often fill the epithelial cells of the nephron.

In elaborating on the varieties of renal disease, much reliance is placed upon the extensive biopsy experience of Kark and his colleagues.[79] Their paper contains an authoritative bibliography also.

Common causes of the nephrotic syndrome

I. Glomerulonephritis. Clinical tradition supports the belief that a small proportion (10 to 15 per cent ?) of patients with acute glomerulonephritis of the hemorrhagic and proliferative type pass through a phase of nephrotic edema on their way to total renal failure.[34]

II. Glomerulosclerosis.

1. IDIOPATHIC. Since the lesion is occasionally seen in newborn infants,[58,125a,158] the responsible agent(s) must pass through the placental barrier; it has been suggested that the mother may produce antibodies against the fetal kidney. The etiology of the postnatal variety is unknown but there is circumstantial evidence which suggests that immune reactions may be responsible. External agents are theoretically able so to modify renal proteins or mucopolysaccharides that they become antigenic; fixation of the autoantibody in glomerular basement membrane then produces the lesion.[98] This theory of autoimmunization is attractive but unproved.

2. METABOLIC. (a) diabetes mellitus;

(b) disseminated lupus erythematosus; (c) amyloidosis; (d) myelomatosis; (e) eclampsia.

3. INFECTIOUS. (a) hemolytic streptococci; (b) other bacteria; (c) syphilis; (d) quartan malaria.

4. CHEMICAL. (a) heavy metals (bismuth, gold, mercury particularly); (b) anticonvulsant drugs (trimethadione, paramethadione, tridion particularly); (c) bee or wasp venom; (d) poison oak, poison ivy; (e) pollens; (f) serum.

5. CONGESTIVE. (a) thrombosis of renal vein; (b) constrictive pericarditis.

6. MISCELLANEOUS. Polyarteritis nodosa, Henoch-Schönlein purpura, sickle cell disease, pyelonephritis, and arteriosclerosis have been described, but the association may be fortuitous.

The experimental counterparts

I. Antikidney serum nephritis (*AKS*). Although certain strains of group A streptococci (types 12, 18, and 25 particularly) are the most frequent cause of proliferative glomerulonephritis in man, attempts to reproduce the disease in animals by injecting them with nephritogenic strains succeed only occasionally.[130] Although others had worked with AKS before him (Lindemann, 1900, and Pearce, 1904), it was Masugi who showed, in 1933, that something very much like the human disease could be produced with it.[97] His technique is in all essentials still the standard one in use today. The serum is made by injecting crude saline extracts of kidney from one species (often the rat) into another species (often the rabbit), either intramuscularly or intraperitoneally; after an interval which permits maximal formation of antibodies the recipient animal is bled and its serum injected back into fresh animals of the first species. On the basis of the potency of the serum and other factors not well understood, these animals soon develop proteinuria, hypoproteinemia, edema, hypertension, lipemia, and azotemia to a variable degree. The resulting picture is therefore a mixture of "nephritis" and "nephrosis." The evidence shows that the rat is more likely to develop the nephrotic syndrome than the dog, which usually becomes uremic.[1] Complete recovery by either species is possible, but death from uremia in a few months is more common.[48,70]

Seegal and Bevans[143] summarize in detail the pathologic and clinical changes. During the first month of the disease the clinical picture corresponds to that seen in acute proliferative glomerulonephritis in human beings; the first visible renal lesion is swelling of the glomerular basement membrane, and this is quickly followed by proliferation of capillary endothelium, thrombosis and necrosis of the glomerular tufts, cellular infiltration of the glomerulus, and a leakage of fibrin and red cells into Bowman's capsule. The tubule cells are swollen and often desquamated, and many casts are seen within the tubule lumens. If the animal survives the first month, the proliferative and exudative reactions subside, but the basement membrane thickens and the intraglomerular capillaries thrombose. With the passage of time, glomeruli become entirely obliterated and "can be recognized as fibrous balls containing varying amounts of hyaline material." Basement membranes become progressively thicker, and fat infiltrates the tubular epithelial cells. The nephrotic syndrome may appear either early or late, and it may disappear spontaneously. The electron microscope shows that an osmophilic exudate very quickly appears between the layers of Bowman's membrane in AKS-treated mice and rats, and that this is followed by swelling of the pedicels and thickening of capillary epithelium,[115,131] a reaction which could represent fixation of antibodies. These structural changes are accompanied by histochemical evidence of alterations in the activity of certain hydrolytic and oxidative enzyme systems.[155] Studies of human material at the University of Minnesota were probably the first which showed the constancy of the podocytic lesions in various types of nephrotic children,[41,154] and similar changes have been described by Kark's group in Chicago.[44] Excessive amounts of globulin (antibody ?) in the glomeruli and around the tubules of patients with a wide variety of kidney diseases have been found by means of the fluorescein-staining technique,[51,98,125b,125c] but the meaning of this is unclear. Krakower and his colleagues[63,86] have presented evidence that the glomerular basement membrane is the most potent source of antigen, and a number of laboratories

have shown that labeled globulins concentrate most intensely in the glomeruli,[30,36] possibly because of the enormous quantity of blood which normally irrigates these structures. The problems are extremely complex, however, because both the kidney extracts and their antisera are obviously impure. A common antigen probably occurs in many tissues. Any interpretation of this phenomenon must recognize the fact that there is usually a latent period of a few days between the injection of AKS and the appearance of renal disease. The lesions may not be due to fixation of renal antibodies therefore, but to the fixation of antibodies evoked in the rat against the injected serum of the rabbit[81] or to a gamma-globulin in it.[124b] Further intricacies arise from the fact that the union of antigen and antibody may so alter the gamma-globulin molecules involved that the new complex itself becomes antigenic and able to invoke its own immune response; theoretically, at least, this process of continued protein denaturation and autoimmunization could go on indefinitely. Human renal disease has been explained analogously by the supposition that many foreign substances—streptococcal products, for example[27]—may so alter the renal proteins of susceptible individuals as to make them antigenic, but no one has consistently found renal antibodies in the serum of patients with kidney disease.[124c] Since adrenocortical steroids modify immune reactions, it may be important to note that Goodman and associates[63] found that renal tubular epithelial cells and glomerular epithelial cells have antigens in common. Nephrotic rat kidney has increased proteolytic activity,[65] and enzymes may themselves be antigenic.[113] It should also be noted that not many workers have used true autoantibodies, although they have often called them such; they have usually used homoantibodies instead, so that there is some question of a foreign protein reaction within the same species. Heymann is one of the few who has attempted to produce nephritis in uninephrectomized rats with preparations made from the animal's own excised kidney; he found that a mixture of kidney protein and Freund's adjuvant is an effective agent.[72]

II. Chemical nephritis.

1. AMINONUCLEOSIDE. Metcoff and colleagues[49] first reported that a derivative of the antibiotic ***puromycin*** can produce the nephrotic syndrome in animals. The active substance (3, 6-dimethylamino purine-3-amino-D-ribose) is made by removing a molecule of tyrosine from a molecule of Puromycin. It is evidently not a simple protoplasmic poison because there is a definite latent period between the time of administration and the appearance of proteinuria, even after intravenous injection. Thickening of the foot processes and the basement membranes[125c] occurs, and chronic renal disease can be produced by repeated administration, but the syndrome is reversible. Recant and colleagues reported that the earliest changes detectable by the electron microscope were in the podocytes,[66] and that these changes were associated with inhibition of the formation of ATP, suggesting abnormalities in nucleoprotein metabolism[129] as a factor in the disease in rats. Hartman[68] reviewed her work and that of others which indicates that the glomerular lesion may be due to an antimetabolite resembling adenosine. No evidence of antibody formation has yet been found. Harms[65] found that slices of tissue from such kidneys exhibited increases in catheptic activity similar to those shown by slices from AKS-treated animals.

Corticosteroids have an uncertain ameliorating effect upon nephropathy due to AKS, and none upon that due to aminonucleoside.[1]

2. TRIDIONE. A few epileptics have become edematous while taking certain anticonvulsant drugs, and rats given large doses of Tridione for many months have developed glomerulosclerosis and proteinuria but no edema.[125g]

3. IRON OXIDE. Saccharated iron oxide has produced a similar syndrome in rabbits.[125f]

Differential diagnoses

Recognition of the nephrotic syndrome is no problem even in the absence of edema if a heavy continuous proteinuria prompts the physician to look for the characteristic changes in urine and blood. The real difficulty comes only too often when he tries

to find the cause, and from its detection to say something about treatment and prognosis.

As in other areas the history is all-important, particularly as to contact with mercury in the form of diuretics[111] or teething powder,[156] bismuth,[11] bee venom,[136] poison oak,[137] poison ivy,[125i] and anticonvulsant drugs.[159] Serum, pollens, trichorethylene, and gold have also been implicated, and the syndrome has occurred during such infectious disorders as quartan malaria,[82] secondary syphilis, diphtheria, and subacute bacterial endocarditis.[79] A very small number of nephrotic adults give a history of acute hemorrhagic glomerulonephritis, a disease also uncommon in children under 5 years of age. When the fact is considered that the average American child has four or five colds per year, it is difficult to relate ordinary infections of the respiratory tract to the appearance of edema. Bloom and Seegal[21] found that about half of their patients who died of renal failure had passed through a nephrotic phase, but that neither pyelonephritis nor renal arteriolosclerosis bore any causal relationship to the nephrotic syndrome, a fortunate circumstance which simplifies the diagnostic difficulties appreciably.

Renal function tests of even the most refined nature measure the *extent* of disease rather than its *kind* and give no prognostic aid at all unless repeated at enough intervals to afford some estimate of the tempo of the process. Intense proteinuria is characteristic of all varieties of the nephrotic syndrome and may be massive in patients whose glomeruli show minimal disease. Red cells are usually scarce but gross hematuria occurs at times. In the early stages, casts, hyaline or granular, may be surprisingly rare. The important element in urinary sediment is the *fat body*, deposits of cholesterol esters in leukocytes, epithelial cells or casts which show up so well in polarized light as doubly refractile Maltese crosses. These are not pathognomonic for the nephrotic syndrome but are more numerous in hyperlipemic states.[139] Pyuria is seen in noninfectious lesions, such as lupus erythematosus, so that the appearance of excessive numbers of leukocytes and "glitter cells," even in clumps, should not be equated with bacterial disease; bacteria in casts, however, give certain evidence of renal infection. The broad casts of renal failure are more often seen in the urine of patients who also have azotemia and hypertension. Schreiner has recognized a wide spectrum of formed elements in the urine of patients with the collagen diseases.[140]

The introduction of paper electrophoresis about 1950, was a major advance beyond the older chemical techniques for estimating "albumin-globulin ratios," but the significance of the variable globulin patterns in the sera of patients with renal diseases is not yet clear. The proteins which escape most easily into the urine ($alpha^1$-globulin, gamma-globulin, transferrin, ceruloplasmin, albumin) are those whose molecular weights are less than 200,000, and these are apt to be scarce in the plasma.[150] The larger molecules are excreted with more difficulty, so that the concentrations of $alpha^2$-globulin, beta-lipoprotein, and fibrinogen in serum are usually high. Since the urine of nephrotic patients is essentially fat-free, some dissociation of lipoproteins probably takes place in the kidney, but we, like others, have been unable to detect any useful correlation between the globulin-partition pattern and the structural changes in the kidney, except that an increased amount of gamma-globulin is more commonly found when the nephrotic syndrome is due to some systemic disease, such as lupus erythematosus, rather than to simple glomerulosclerosis. Lipoproteins are often abnormal, moving between the α and β peaks of normal serum.[88]

Renal biopsy. Since treatment and, hence, prognosis depend upon precise diagnosis, needle biopsy of the kidney is often a justifiable procedure, particularly among young patients who are neither hypertensive nor uremic. Large numbers of biopsies on nephrotic patients have been reported from Scandinavia,[16] England,[77] Washington,[141] and Chicago.[79] The wide variety of lesions found in the 98 cases so studied by Kark[79] is impressive. Only about one half of these cases were diagnosed pathologically as some sort of glomerulonephritis (usually membranous but sometimes proliferative or both); 18 patients had lupus erythematosus, 15 were diabetics, 3 had

amyloidosis, and in 11 the only glomerular lesions were in the podocytes. The importance of this lesion is its reversibility by hormonal therapy,[17,32,45,46] whereas the renal lesions which accompany such metabolic disorders as diabetes mellitus, disseminated lupus erythematosus, or amyloidosis are notoriously refractory to steroid treatment. The decision to perform a biopsy or not must be made in each case on its own merits, for some danger attends even in the hands of experts.

Associated diseases

It is not enough to arrive at a diagnosis of the nephrotic syndrome. Effort must be made to identify associated disorders which are frequent and sometimes curable.

Chronic proliferative glomerulonephritis. In acute glomerulonephritis of streptococcal origin, electron microscopy shows, as anticipated, marked edema of both the endothelial and epithelial components of Bowman's membrane, together with an accumulation of basement membrane-like material between the proliferating endothelial cells; it is this which obliterates glomeruli in chronic disease, but changes in the podocytes are minimal.[125I]

Disseminated lupus erythematosus. A valuable three-dimensional view of the natural history of lupus nephropathy is afforded by Kark's extensive biopsy studies.[107,120] These suggest that nearly all patients who live long enough will exhibit the nephrotic syndrome, and, of course, uremia is a common terminal event. The disease begins in the glomerular capillaries with an irregular focal thickening of the basement membrane. Adjacent endothelial cells proliferate, and deposition of fibrinoid within the capillary walls gives to it a smudgy, eosinophilic appearance. "Wire-loop" lesions are simply focal collections of fibrinoid. Hematoxylin-bodies, hyaline thrombi, and glomerular sclerosis develop later, if at all. It is the combination of lesions rather than the appearance of any one of them which establishes the diagnosis. Systemic evidence of lupus often subsides as renal failure proceeds, in which event the urinary sediment may offer an important diagnostic clue. Krupp[87] showed that in patients with lupus and polyarteritis nodosa the urine often contains formed elements of great variety: red blood cells and red cell casts suggest the existence of acute glomerulitis; oval fat bodies, hyaline casts, and heavy proteinuria are hallmarks of the nephrotic syndrome, and broad casts from the ducts of Bellini usually indicate renal failure. Schreiner[140] has emphasized the importance of these "telescoped" urinary sediments but warns that they are not entirely specific. Renal biopsy is a particularly useful procedure because the prognosis in lupus nephritis is much more serious than in membranous glomerulosclerosis.

Diabetes mellitus. In 1936, Kimmelstiel and Wilson[84] described *nodular* deposits of a hyaline material in the peripheral portion of glomeruli of patients with chronic diabetes mellitus. Twenty years later, Kimmelstiel[85] reaffirmed the specificity of this lesion and described similar deposits in the parietal layer of Bowman's membrane and the basement membrane of tubular epithelium. He agreed with Bell,[13] however, that *diffuse* glomerulosclerosis is a much more common lesion, and the one related to edema and hypertension. From a large biopsy experience, Kark's group[55,56] concluded that the nodular variety is never found in the absence of the diffuse lesion, and that it correlates poorly with the clinical signs of diabetic nephropathy. They point out that technically this is not a sclerosing lesion but one which is due to the deposition of mucopolysaccharides, a reflection of the underlying metabolic disturbances. The term "intercapillary glomerulosclerosis" should be abandoned, for the electron microscope shows that the essential lesion consists of thickening of the capillary basement membrane, together with deposition of mucoproteins within the endothelial cells,[14] although others[125I] found the hyaline deposits between the endothelial cells. The diabetes is often so mild that a glucose tolerance test may be necessary to establish its coexistence.[7,50] The presence of oval fat bodies in the urine and of capillary aneurysms in the retina are important diagnostic aids, since nephrosclerosis and pyelonephritis are also common in diabetes mellitus.[91] Effective prophylaxis or treatment do not exist.

Amyloid. In primary amyloidosis, ab-

normal proteins are irregularly deposited in the basement membranes of the glomeruli and tubules and in the walls of small arteries, and the glomerular epithelium is also diseased in a spotty, irregular manner.[108,1251] Movat's studies[105] with the electron microscope on human biopsy material showed deposition of amyloid on both sides of an intact basement membrane, together with fusion or destruction of the podocytes. Amyloidosis secondary to myeloma and chronic infection is distributed similarly.[54] Biopsy is the only reliable way of making the diagnosis of either variety, and it is important that it be made, since amyloidosis does not respond to treatment.

Pregnancy. Thickening of the basement membrane with deposition of fibrinoid material on the endothelial side are commonly found in pregnant women with hypertensive cardiorenal disease, but the specific lesion of eclampsia is swelling of the capillary endothelium.[119,1251,146] This is entirely reversible but the other changes are not. Disease of the podocytes does not occur. It has been suggested that true eclampsia is due to the fact that mother and fetus are antigenically incompatible in the sense that the mother's blood contains a protein which the child does not have and which therefore produces antibodies to it through the placental circulation—a sort of Masugi experiment in reverse.[117] This theory is unproved but can account for the fact that the mother gets kidney disease but the child does not. In any event, pure eclampsia leaves no residual renal damage.

Venous congestion of the kidney. Chronic congestive heart failure from any cause, and constrictive pericarditis in particular, is occasionally associated with massive proteinuria and its sequelae; in the latter situation, pericardiectomy has been curative.[20,67] "Podocyte disease" has been seen.[1251] Bilateral thrombosis of the renal veins is a fairly common complication of inferior vena caval thrombosis[20,67,118] and may be suspected after physical examination alone. When no signs of caval obstruction coexist, its detection may require an attempt to fill the renal veins with radiopaque material during a Valsalva maneuver. Spontaneous thrombosis of the small interlobular veins also occurs in the course of various renal diseases, but this is a diagnosis which only the pathologist can make. Massive infarction of the kidney due to venous thrombosis happening so quickly that collateral circulation cannot form occurs especially in children. The clinical picture is usually that of acute renal failure. It is well to remember that the normal renal blood flow is about one fourth of cardiac output.

Other diseases. The nephrotic syndrome has been seen occasionally in polyarteritis nodosa, multiple myeloma, Henoch-Schönlein's purpura, sickle cell anemia, and arteriolar nephrosclerosis,[79] but these examples are so rare as to raise the question of random coexistence.

Treatment

Since *edema* is usually the most striking abnormality, both the patient and his physician may easily become so preoccupied with its control that the more fundamental disturbances are neglected. Anasarca, however, is largely a cosmetic problem, and there is no evidence that the "dry nephrotic" is better off than the "wet" one, although he may have less mechanical discomfort. The therapeutic target should be the abolition of proteinuria rather than the promotion of the flow of urine. If the renal lesion cannot be resolved, however, it is the physician's next duty to maintain optimal nutrition, to prevent intercurrent infection, and to manage the erosions of cardiorenal function as they inevitably appear.

Diuretics. Bed rest for a time and moderate restriction of the intake of salt often reduce edema quite appreciably, even in the face of persistent hypoalbuminemia. Xanthines, mercurials, and carbonic-anhydrase inhibitors are less popular than they were before the introduction of the thiazide and phthalimidine derivatives. In such a rapidly expanding field as this, any recommendation can have only temporary validity, but at the time of this writing the following compounds are widely used: chlorothiazide (Diuril), hydrochlorothiazide (Esidrex, Hydrodiuril, Oretic), trichlormethiazide (Naqua), methylchlorothiazide (Enduron), flumethiazide (Ademol), hydroflumethiazide (Saluron), benzydroflumethiazide (Naturetin), and chlorthali-

done (Hygroton). We,[83] among many others, have obtained satisfactory responses to 50 mg. of hydrochlorothiazide twice daily, and prefer it to mercurial compounds, since it induces parallel increases in the output of sodium and chlorides without inordinate loss of potassium. In addition to hypokalemia with its attendant muscular weakness and cardiac arrhythmias, thiazide derivatives may cause hypochloremic alkalosis, hyponatremia, and hyperuricemia, with or without clinical gout.[47] They have on occasion also produced bone-marrow depression, jaundice, vomiting, and dermatitis.

Nephrotic patients react less dramatically on the whole, however, than do patients with congestive heart failure. Steroids which block the action of aldosterone at the renal level (spironolactones such as Aldactone) may be used in conjunction with the above-mentioned diuretics in order to intensify the rate of sodium excretion, and prednisolone may also be added if the patient is hyponatremic as well. Rigorous restriction of the intake of sodium, especially if augmented by cation exchange resins, is apt to accentuate the hyponatremia so regularly seen anyway. Hypertonic saline only increases blood volume and aggravates the edema.

Plasma volume expanders. These materials have been more useful as physiologic tools than as therapeutic agents, but in selected instances may usefully potentiate the actions of steroids and diuretic drugs alike. Human albumin is expensive, and much of it is promptly excreted in the urine.[29,93,94] Plasma substitutes are cheaper and equally effective[75] but have inherent drawbacks of their own. Acacia, widely used for a time, was abandoned when deposits were found in the liver long after administration. Dextran and polyvinylpyrrolidone have been criticized on the same grounds,[127] and the former particularly has caused allergic reactions, renal damage and abnormal bleeding. All substitutes for the patient's own plasma proteins will be effective only when his capillaries are tight enough to permit what Armstrong has called an "iso-osmotic" response characterized by hemodilution.[5] Human blood and its derivatives are all subject to viral contamination, and the physician must balance the temporary benefit accruing from the use of substitutes against their small but measurable toxic properties.

Other agents. Occasionally, diuresis has followed the deliberate induction of measles[76] and malaria[57] and short courses of nitrogen mustard.[152] The rationale for their use is tenuous, and their real value very much in doubt. Intravenous calcium gluconate may be a mildly useful adjunct to steroid therapy by an unknown mechanism.[33] Desiccated thyroid was once administered because the basal metabolic rate is low and the serum lipids high in nephrotic patients, but nephrotic patients tolerate large doses of this material without apparent harm or benefit. Heparin has also been used because of its capacity to disburse blood lipids, but this is yet in the experimental stage.

Hormones. ACTH and adrenocortical steroids are, by common consent, the only agents which can suppress the disease and prolong life.[8,95] The modus operandi of these substances is unknown, but their diuretic properties must be due to an increase in glomerular filtration rate relative to the rate of tubular resorption of sodium, whereas the abatement of proteinuria may be attributed in part to their anti-inflammatory effects upon the glomerular filter, but in greater part to poorly understood metabolic processes. For example, ACTH increases the tubular transportation not only of uric acid and phosphorus but of ammonia and hydrogen, too; so it evidently participates in important enzymatic reactions.[69] No unifying concept has yet been evolved which satisfactorily coordinates these apparently dissimilar actions. About all that one can say at present is that diuresis often begins before any rise in plasma oncotic pressure occurs, that it may be independent of any change in protein excretion, that it is accompanied by a drop in the output of aldosterone, that steroids can normalize early lesions in the epithelial layer of Bowman's membrane, and that abolition of proteinuria is paralleled by a rise in the concentration of serum protein and by a fall in the concentration of serum lipids. Lange[89,90] and Merrill[99,100] have been especially influential in establishing schedules which call for prolonged treatment with high doses, although differences of

opinion exist regarding the relative virtues of one agent over another. If ACTH is physiologically superior, it is also less convenient, for it cannot be taken by mouth. Patients—and therefore probably most physicians—prefer the steroids, which can be swallowed. Prednisone, prednisolone, methylprednisolone, and triamcinolone appear to be equally effective,[125i] and all are superior to cortisone or hydrocortisone in that they are less apt to produce electrolyte disturbances, hyperglycemia, hypertension, convulsions, peptic ulceration, mental disturbances, and osteoporosis.

The schedule must be tailored to the patient's need, but the plan advised by Piel and Williams[116] offers a satisfactory rule of thumb. It calls for either ACTH gel or prednisone in a daily dose of 1 mg. per pound of actual body weight until diuresis occurs and proteinuria has been suppressed for 1 week. At this point, treatment is limited to 3 consecutive days of each week, and the dose is gradually reduced to a basal level of 20 mg. daily and held there until the urine has been protein-free for about 1 year.* This of course represents the ideal program, one to which perhaps 80 per cent of children and adults will respond, although it is rather easier to render patients edema-free than it is to control the proteinuria.

What of the resistant patient? Induced hyperadrenocorticism is a severe metabolic dislocation, and the physician must ask himself whether slight amelioration of the renal lesion is worth the price. We have not used the high doses continuously for more than 6 weeks. Sometimes, diuresis does not occur until the treatment is stopped, for reasons that may be related to temporary adrenal insufficiency. The majority of patients will lose a satisfactory amount of edematous fluid, but the few in whom proteinuria is unmodified require re-treatment after a short interval of rest—*provided* that the physician has done what he can to rule out such unresponsive diseases as lupus erythematosus, amyloidosis, or diabetes mellitus. Obviously, renal biopsy is of great value here. In Lange's hands,[90] 88 per cent of 42 children and 68 per cent of 19 adults diuresed satisfactorily in the first course of treatment, and all but one of the resistant cases responded to retreatment, one patient requiring five courses. Usually, the dosage is increased in subsequent courses, and nitrogen mustard may be added to the steroid program. Mild azotemia and hypertension are not absolute contraindications. About 60 per cent of these cases were kept aproteinuric on intermittent steroid maintenance therapy. Merrill[100] also reported encouraging results from continuous treatment with ACTH gel. In so far as we know, hormonal therapy has not abolished proteinuria in patients who failed to diurese. Danowski, Mateer and Puntereri,[31] however, were able to abolish proteinuria in only 15 per cent of 54 miscellaneous cases of persistent proteinuria, but reported good results in about one third of the patients with glomerulonephritis and membranous glomerulosclerosis.

It may be useful to teach the patient on maintenance therapy to test his own urine for protein, either with 20 per cent sulfosalicylic acid or Clinitest papers. Proteinuria commonly increases during such stressful episodes as respiratory infections, sunburn, immunization procedures, severe physical exercise, etc., but very likely it is unnecessary to increase hormone dosage unless concomitant gain in weight occurs. A sliding scale may be worked out whereby the dosage is adjusted according to the degree of proteinuria, much as a diabetic patient adjusts his ration of insulin according to the degree of glucosuria. The relapse rate in the nephrotic syndrome is quite high unless treatment is meticulously adjusted to the patient's particular needs, and relapse may occur after years of clinical and laboratory control. Only when the patient has been virtually aproteinuric for about a year is it permissible to discontinue treatment, and this must be done by a very gradual reduction in hormone dosage over a period of 3 to 6 months.

Diet. Although Epstein mistakenly attributed the proteinuria to thyroid dysfunction, he was probably the first clinician to appreciate the relationship between pro-

*Potassium chloride (2 to 4 Gm.) and oral penicillin (250,000 units) should also be given on each day that large doses of hormone are used. Occasionally, a salt-poor diet is needed to control edema, and some administer aluminum hydroxide gel by mouth to reduce gastric acidity.

teinuria, hypoproteinemia, and edema,[43] and his advice concerning a high intake of protein is still heeded.[39] Diets very rich in protein are not well tolerated by children especially, and in any case no marked effect upon concentration of serum albumin need be expected, but even slight increase in retained nitrogen is useful; anabolic steroids are theoretically useful from this standpoint also but have not been thoroughly evaluated yet in patients with serious renal disease. Carbohydrate is usually welcomed by the patient. Intake of salt and water ordinarily need not be much restricted. Fruit juices are rich in the potassium needed especially during steroid treatment. The important thing is a diet which maintains body weight and which is acceptable to the patient.

Physical activity. Prolonged bed rest is contraindicated. There is no reason why the patient should not do whatever he can do easily, although the renal vasoconstriction which normally occurs in the erect position and during exercise may be an argument in the minds of some for a nap after meals and for a long night's rest. The susceptibility of nephrotic patients to bacterial disease is probably an argument against hospitalization these days, although initial studies and treatment with ACTH may require it.

Statistics concerning the effect of treatment upon mortality have only temporary value. Evaluation is further complicated by failure of many authors to distinguish the varieties of glomerular disease which are associated with the nephrotic syndrome.[112] The recognition of disease of the basement membrane as an entity different from the proliferative endothelial response to streptococcal infections is a relatively recent achievement and makes it difficult to interpret even such important contributions as the classic study by Addis.[2]

Whereas it is now generally conceded that the outlook for patients with poststreptococcal glomerulonephritis is quite good, only the dimmest outline of the natural history of the nephrotic syndrome is available. Perhaps the best account of what happens to patients when the nephrotic syndrome is unaccompanied by systemic disease in the pre-steroid era is a series from the Hospital of the Rockefeller Institute[8]; about half of the children recovered spontaneously, but adults did so rarely. Among those who did so, the duration of the disease varied from 4 to 157 months, the mean duration being 2 to 4 years, depending upon the age group. Among those who died, the duration in the various age groups ranged from 29 to 82 months, but individual variations ranged from 2 to 192 months. This study suggested that urea clearance was a useful prognostic guide in individual cases; recovery was improbable unless the clearance returned to normal. The common causes of death were infection, heart failure, cerebral edema, and venous thrombosis. Rather surprisingly, the introduction of antibiotics had little effect upon survival rate.[144]

The impact of hormonal therapy is authoritatively discussed in each Annual Conference on the Nephrotic Syndrome published by the National Kidney Foundation. At the meeting in 1958, Riley[125k] reported that 75 per cent of 554 children treated intensively were alive 4 years after the onset of the syndrome, whereas only 60 per cent of 318 control patients survived a similar length of time, and that a greater proportion of the living were in complete or partial remission. Goodman and Baxter[62] obtained equally good results in adults and children; at least partial remissions occurred in three fourths of each group. Post and Eckel[121] emphasized the fact that adults with the nephrotic syndrome have a much wider variety of degenerative renal lesions than do children, and thought that less than 50 per cent of adults with the idiopathic variety respond satisfactorily. Nevertheless, they believed that all such patients should receive intensive therapy for at least 3 to 4 months, and that prolonged maintenance therapy in those who do respond is necessary to prevent relapse. Not enough is known about the natural history of the disease, however, to justify dogmatic statements about possible effects of treatment upon long-term survival.

Summary

The nephrotic syndrome is apparently due to continued excretion (and destruction ?) of serum albumin by the kidney. The chief clinical consequences are proteinuria, hypoalbuminemia, edema, lip-

emia, and susceptibility to infection and, all too often, to terminal renal failure.

The nephrotic syndrome is associated with many renal diseases. The most constant structural changes are seen by electron microscopy in the glomerular epithelium. A reasonable facsimile of the disorder can be produced in animals by anti-kidney serum and by certain chemicals, notably aminonucleoside. The theory that it is due to the formation of autoantibodies is attractive but unproved.

REFERENCES

1. Adams, D. A.: The pathophysiology of the nephrotic syndrome, Arch. Int. Med. **106**:117, 1960.
2. Addis, T.: Glomerular nephritis, diagnosis and treatment, New York, 1948, The Macmillan Co.
3. Albright, F., Bartter, F. C., and Forbes, A. P.: The fate of human serum albumin administered intravenously to a patient with idiopathic hypoalbuminemia and hypoglobulinemia, Tr. A. Am. Physicians **62**:204, 1946.
4. Allen, A. C.: The clinicopathologic meaning of the nephrotic syndrome, Am. J. Med. **18**:277, 1955.
5. Armstrong, S. H., Jr.: Mechanisms of action of serum albumin in internal medicine, Am. J. Med. **4**:390, 1948.
6. Armstrong, S. H., Jr., Kark, R. M., Schoenberger, J. A., Shatkin, J., and Sights, R.: Colloid osmotic pressures of serum proteins in nephrosis and cirrhosis; relations to electrophoretic distributions and average molecular weights, J. Clin. Invest. **33**:297, 1954.
7. Arnold, J. D., Tarlove, A. R., Spargo, B., and Brewer, G. J.: Subclinical diabetes mellitus in patients presenting with clinical chronic "glomerulonephritis," Tr. A. Am. Physicians **71**:186, 1958.
8. Barnett, H. L., and Eder, H. A.: The nephrotic syndrome, J. Chron. Dis. **5**:108, 1957.
9. Barnett, H. L., Forman, C. W., and Lawson, H. D.: The nephrotic syndrome in children, Advances Pediat. **5**:53, 1952.
10. Baxter, J. H., Goodman, H. C., and Havel, R. J.: Serum lipid and lipoprotein alterations in nephrosis, J. Clin. Invest. **39**:455, 1960.
11. Beattie, J. W.: Nephrotic syndrome following sodium bismuth tartrate therapy in rheumatoid arthritis, Ann. Rheumat. Dis. **12**:144, 1953.
12. Bell, E. T.: A clinical and pathological study of subacute chronic glomerulonephritis, including lipoid nephrosis, Am. J. Path. **14**:691, 1938.
13. Bell, E. T.: Renal diseases, ed. 5, Philadelphia, 1946, Lea & Febiger.
14. Bergstrand, A., and Bucht, H.: Electron microscopic investigations on glomerular lesions in diabetes mellitus (diabetic glomerulosclerosis), Lab. Invest. **6**:292, 1957.
15. Berman, L. B., and Schreiner, G. E.: Clinical and histologic spectrum of the nephrotic syndrome, Am. J. Med. **24**:249, 1958.
16. Bjørneboe, M., Brun, C., Gormsen, H., Iversen, P., and Raaschou, F.: The nephrotic syndrome. I. Histological changes illustrated by means of biopsy of the kidney, Acta. med. scandinav. (Suppl. 266) **142**:233, 1952.
17. Bjørneboe, M., Brun, C., Gormsen, H., Iversen, P., and Raaschou, F.: The nephrotic syndrome. II. The effect of corticotrophin (ACTH), Acta med. scandinav. (Suppl. 266) **142**:249, 1952.
18. Blackman, S. S., Jr.: On the pathogenesis of lipoid nephrosis and progressive glomerulonephritis, Bull. Johns Hopkins Hosp. **57**:70, 1935.
19. Blahd, W. H., Fields, M., and Goldman, R.: The turnover rate of serum albumin in the nephrotic syndrome as determined by I^{131}-labeled albumin, J. Lab. & Clin. Med. **46**:747, 1955.
20. Blainey, J. D., Hardwicke, J., and Whitefield, A. G. W.: The nephrotic syndrome associated with thrombosis of the renal veins, Lancet **2**:1208, 1954.
21. Bloom, W. L., and Seegal, D.: The nephrotic phase: its frequency of occurrence and its differential diagnostic value in determining the nature of the renal lesion in 120 patients who died of renal failure, Ann. Int. Med. **25**:15, 1946.
22. Borst, J. G.: The maintenance of an adequate cardiac output by the regulation of the urinary excretion of water and sodium chloride; an essential factor in the genesis of edema, Acta. med. scandinav. (Suppl. 207) **130**:1, 1948.
23. Bradley, S. E., Bradley, G. P., Tyson, C. J., Curry, J. J., and Blake, W. D.: Renal function in renal diseases, Am. J. Med. **9**:766, 1950.
24. Bradley, S. E., and Tyson, C. J.: The "nephrotic syndrome," New England J. Med. **238**:223, 1948.
25. Broch, O. J., and Brodwall, E.: Urinary proteins in renal diseases, Acta. med. scandinav. **160**:353, 1958.
26. Cartwright, G. E., Bubler, C. J., and Wintrobe, M. M.: Studies on copper metabolism. XI. Copper and iron metabolism in the nephrotic syndrome, J. Clin. Invest. **33**:685, 1954.
27. Cavelti, P. A.: Pathogenesis of glomerulonephritis and rheumatic fever, Arch. Path. **44**:119, 1947.
28. Chinard, F. P., Lauson, H. D., Eder, H. A., Griff, R. L., and Hiller, A.: A study of the mechanism of proteinuria in patients with the nephrotic syndrome, J. Clin. Invest. **33**:621, 1954.
29. Chinard, F. P., Lauson, H. D., Eder, H. A., and Griff, R. L.: Plasma volume changes following the administration of albumin to patients with the nephrotic syndrome, J. Clin. Invest. 33:629, 1954.
30. Cruikshank, B., and Hill, A. F. S.: The histochemical identification of a connective tissue antigen in the rat, J. Path. & Bact. **66**:283, 1953.

31. Danowski, T. S., Mateer, F. M., and Puntereri, A. J.: ACTH of adrenocortical steroid therapy of proteinuria in adolescents and in adults, Am. J. M. Sc. **237**:545, 1959.
32. Mateer, F. M., Weigand, F. A., Greenman, L., Weber, C. J., Kunkel, G. A., and Danowski, T. S.: Corticotropin (ACTH) therapy of nephrotic syndrome in children, A.M.A. J. Dis. Child. **93**:591, 1957.
33. Dingman, J. F., and Yoffee, H. F.: Effect of calcium gluconate and adrenal steroids on sodium and water excretion in patients with cirrhosis and ascites, New England J. Med. **262**:585, 1960.
34. Earle, D. P., Jr.: Glomerulonephritis, Disease-a-Month, January, 1956.
35. Ehrich, W. E.: Glomerular nephritis and lipid nephrosis with identities and mechanisms, J. Chron. Dis. **5**:14, 1957.
36. Eisen, H. M., Sherman, B., and Pressman, D.: The zone of localization of antibodies. IX. The properties of anti-rat-lung serum, J. Immunol. **65**:543, 1950.
37. Eliasch, H., Sellers, A. L., Rosenfeld, S., and Marmoston, J.: Protein metabolism in the mammalian kidney, J. Exper. Med. **101**:129, 1955.
38. Ellis, A.: Natural history of Bright's disease, Lancet **1**:1, 1942.
39. Epstein, A. A.: The nature and treatment of chronic parenchymatous nephritis (nephrosis), J.A.M.A. **69**:444, 1917.
40. Farquhar, M. G., Vernier, R. L., and Good, R. A.: An electron microscopic study of the glomerulus in nephrosis, glomerulonephritis and lupus erythematosus, J. Exper. Med. **106**:649, 1957.
41. Farquhar, M. G., Vernier, R. L., and Good, R. A.: Studies of familial nephrosis. II. Glomerular changes observed with electron microscope, Am. J. Path. **33**:791, 1957.
42. Farrell, G.: Steroidogenic properties of extracts of beef diencephalon, Endocrinology **65**:29, 1959.
43. Fishberg, A. M.: Hypertension and nephritis, ed. 65, Philadelphia, 1954, Lea & Febiger, p. 445.
44. Folli, G., Pollak, V. E., Reid, R. T. W., Pirani, C. L., and Kark, R. M.: Electron microscopic studies of reversible glomerular lesions in the adult nephrotic syndrome, Ann. Int. Med. **49**:775, 1958.
45. Folli, G., Pollack, V. E., Reid, R. T. W., Pirani, C. L., and Kark, R. M.: Electron microscopic studies of renal biopsies taken from nephrotic patients before and after diuresis, J. Lab. & Clin. Med. **50**:813 (Abst.), 1957.
46. Folli, G., Pollack, V. E., Reid, R. T. W., Pirani, C. L. and Kark, R. M.: Electron microscopic studies of reversible glomerular lesions in the adult nephrotic syndrome, Ann. Int. Med. **49**:775, 1958.
47. Ford, R. V.: Limitations and potential and actual side effects of thiazide derivatives. *In* Moyer, J. H., and Fuchz, M.: Edema—mechanisms and management, Philadelphia, 1960, W. B. Saunders Co., pp. 289-292.
48. Fouts, P. J., Corcoran, A. C., and Page, I. H.: Observations on the clinical and functional course of nephrotoxic nephrosis in dogs, Am. J. M. Sc. **201**:313, 1941.
49. Frenk, S., Antonowicz, I., Craig, J. M., and Metcoff, J.: Experimental nephrotic syndrome induced in rats by aminonucleoside. Renal lesions and body electrolyte composition, Proc. Soc. Exper. Biol. & Med. **89**:424, 1955.
50. Freedman, L. R.: Inapparent diabetes mellitus as a cause of renal insufficiency due to Kimmelstiel-Wilson lesions, Bull. Johns Hopkins Hosp. **100**:132, 1957.
51. Freedman, P., Peters, J. H., and Kark, R. M.: Localization of gamma-globulin in the diseased kidney, Arch. Int. Med. **105**:524, 1960.
52. Freeman, T., and Joekes, A. M.: Nephrotic proteinuria: a tubular lesion? Acta med. scandinav. **157**:43, 1957.
53. Freeman, T., and Mathews, C. M.: Analysis of the behavior of I^{131}-albumin in the normal subject and nephrotic patient, Strahlentherap. Sonderbd. **38**:283, 1958.
54. Geer, J. C., Strong, J. P., McGill, H. C., Jr., and Muslow, I.: Electron microscopic observations on the localization of amyloid in the kidney in secondary amyloidosis, Lab. Invest. **7**:554, 1958.
55. Gellman, D. D., Pirani, C. L., Soothill, J. F., Muehrcke, R. C., and Kark, R. M.: Diabetic nephropathy: a clinical pathologic study based on renal biopsies, Medicine **38**:321, 1956.
56. Gellman, D. D., Pirani, C. L., Soothill, J. F., Muehrcke, R. C., Maduros, W., and Kark, R. M.: Structure and function in diabetic nephropathy. The importance of diffuse glomerulosclerosis, Diabetes **8**:251, 1959.
57. Gilbertson, A. S., and Bashour, F.: Use of malaria therapy in the nephrotic syndrome, J.A.M.A. **160**:25-30, 1956.
58. Giles, H. M., Pugh, R. C. B., Darmady, E. M., Stranack, F., and Woolf, L. I.: The nephrotic syndrome in early infancy: a report of three cases, Arch. Dis. Childhood **32**:167, 1957.
59. Gitlin, D., and Cornwell, D.: Plasma lipoprotein metabolism in normal individuals and in children with nephrotic syndrome, (Abstract) J. Clin. Invest. **35**:706, 1956.
60. Gitlin, D., Janeway, C. A., and Farr, L. E.: Studies on the metabolism of plasma proteins in the nephrotic syndrome. I. Albumin, globulin, and iron-binding globulin, J. Clin. Invest. **35**:44, 1956.
61. Gitlin, D., Cornwell, D. G., Nakasato, D., Oncley, J. L., Hughes, W. L., Jr., and Janeway, C. A.: Studies on the metabolism of plasma proteins in the nephrotic syndrome. II. The lipoproteins, J. Clin. Invest. **37**:172, 1958.
62. Goodman, H. C., and Baxter, J. H.: The nephrotic syndrome. Clinical observations on therapy with prednisone and other steroids, J.A.M.A. **165**:1798, 1957.
63. Goodman, M., Greenspon, S. A., and Krakower, C. A.: The antigenic composition of the various anatomic structures of the canine kidney, J. Immunol. **75**:96, 1955.

64. Gregoire, F., Malmendier, C., and Lambert, P. P.: The mechanism of proteinuria, and a study of the effects of hormonal therapy in the nephrotic syndrome, Am. J. Med. **25**:516, 1958.
65. Harms, W. S.: Unpublished observations.
66. Harkin, J. C., and Recant, L.: The earliest lesion in aminonucleoside nephrosis: an electron microscopic study, (abstract) Am. J. Path **34**:559, 1958.
67. Harrison, C. V., Milne, M. D., and Steiner, R. E.: Clinical aspects of renal vein thrombosis, Quart. J. Med. **25**:285, 1956.
68. Hartman, M. E.: Some metabolic and structural characteristics of experimental nephrosis (editorial), AM. HEART J. **58**:483, 1959.
69. Heidorn, G. H.: The effect of corticotrophin (ACTH) on ammonia production in the nephrotic syndrome, Am. J. M. Sc. **231**:644, 1956.
70. Heymann, W., and Lund, H. Z.: Nephrotic syndrome in rats, Pediatrics **7**:691, 1951.
71. Heymann, W., Gilkey, C., and Lewis, M.: The prognostic significance of globulinuria in the nephrotic syndrome: an electrophoretic study of urinary proteins in the nephrotic syndrome and acute glomerulonephritis, A.M.A. J. Dis. Child **91**:570, 1956.
72. Heymann, W., Hackel, D. B., Harwood, S., Wilson, S. G. F., and Hunter, J. L. P.: Production of nephrotic syndrome in rats by Freund's adjuvants and rat kidney suspensions, Proc. Soc. Exper. Biol. & Med. **100**:660, 1959.
73. Heymann, W., Nash, G., Gilkey, C., and Lewis, M.: Studies on the causal role of hypoalbuminemia in experimental nephrotic hyperlipemia, J. Clin. Invest. **37**:808, 1958.
74. Hooft, C., and Herpol, J.: Aminoaciduria in the course of lipoid nephrosis in children. The influence of ACTH, Acta paediat. **48**:135, 1959.
75. James, J., Gordillo, G., and Metcoff, J.: Effects of infusion of hyperoncotic dextran in children with the nephrotic syndrome, J. Clin. Invest. **33**:1346, 1954.
76. Janeway, C. A.: Diuresis in children with nephrosis: comparison of response to injection of normal human serum albumin and to infection, particularly measles, Tr. A. Am. Physicians **61**:108, 1948.
77. Joekes, A. M., Heptinstall, R. H., and Porter, K. A.: The nephrotic syndrome. A study of renal biopsies in 20 adult patients, Quart. J. Med. **27**:495, 1958.
78. Kaitz, A. L.: Albumin metabolism in nephrotic adults, J. Lab. & Clin. Med. **53**:186, 1959.
79. Kark, R. M., Pirani, C. L., Pollack, V. E., Muehrcke, R. C., and Blainey, J. D: The nephrotic syndrome in adults: a common disorder with many causes, Ann. Int. Med. **49**:751, 1958.
80. Kark, R. M., Pirani, C. L., Pollack, V. E., Muehrcke, R. C., and Blainey, J. D.: The nephrotic syndrome in adults: a common disorder with many causes, Ann. Int. Med. **49**:751, 1958.
81. Kay, C. F.: The mechanism of a form of glomerulonephritis. Nephrotoxic nephritis in rabbits, Am. J. M. Sc. **204**:483, 1942.
82. Keitel, H. G., Goodman, H. C., Harel, R. J., Gordon, R. S., and Baxter, J. H.: Nephrotic syndrome in congenital quartan malaria, J.A.M.A. **161**:520, 1956.
83. Kemp, J. A., and Findley, T.: The choice of a diuretic, with special reference to hydrochlorothiazide, J. M. Assn. Georgia **48**:389, 1959.
84. Kimmelstiel, P., and Wilson, C.: Intercapillary lesions in the glomeruli of the kidney, Am. J. Path. **12**:83, 1936.
85. Kimmelstiel, P.: Glomerulosclerosis, J. Mt. Siani Hosp. **23**:657, 1956.
86. Krakower, C. A., and Greenspon, S. A.: Localization of the nephrotoxic antigen within the isolated renal glomerulus, A.M.A. Arch. Path. **51**:629, 1951.
87. Krupp, M. A.: Urinary sediment in visceral angiitis (periarteritis nodosa, lupus erythematosus, Libman-Sacks disease): quantitative studies, Arch. Int. Med. **71**:54, 1943.
88. Kunkel, H. G., and Slater, R. J.: Lipoprotein patterns of serum obtained by zone electrophoresis, J. Clin. Invest. **31**:677, 1952.
89. Lange, K., Strang, R., Slobody, L. B., and Wenk, E. J.: The treatment of the nephrotic syndrome with steroids in children and adults, Arch. Int. Med. **99**:760, 1957.
90. Lange, K., Wasseman, E., and Slobody, L. B.: Prolonged intermittent steroid therapy for nephrosis in children and adults, J.A.M.A. **168**:377, 1958.
91. Leiter, L.: The capillary vascular lesion in diabetes mellitus. Its clinical manifestations and significance, Diabetes **4**:280, 1955.
92. Longcope, W. T.: Some observations on the course and outcome of hemorrhagic nephritis, Internat. Clinics (new series) **1**:1, 1938.
93. Luetscher, J. A., Jr., Hall, A. D., and Kremer, V. L.: Treatment of nephrosis with concentrated human albumin. I. Effects on the proteins of body fluids. J. Clin. Invest. **28**:700, 1949.
94. Luetscher, J. A., Jr., Hall, A. D., and Kremer, V. L.: Treatment of nephrosis with concentrated human serum albumin. II. Effects on renal function and on excretion of water and some electrolytes, J. Clin. Invest. **29**:896, 1950.
95. Luetscher, J. A., Jr., and Mulrow, P. J.: The nephrotic syndrome, Disease-a-Month, August, 1956.
96. Martin, N. H.: Primary protein deficiencies, with special reference to the specific plasma aproteinemias, Lect. Sci. Basis Med. **5**:165, 1955-56.
97. Masugi, M.: Über die experimentelle Glomerulonephritis durch das specificische antinieren Serum, Beitr. path. Anat. **92**:429, 1933.
98. Mellors, R. C., and Ortega, L. G.: New observations on the pathogenesis of glomerulonephritis, lipid nephrosis, periarteritis nodosa and secondary amyloidosis in man, Am. J. Path. **32**:455, 1956.
99. Merrill, A. J.: Use of steroids in renal disease, Tr. Am. Clin. & Climatol. A. **68**:193, 1956.

100. Merrill, A. J., Wilson, J., and Timberlake, L. F.: Continuous therapy of nephrotic syndrome in children with corticotrophin gel, Arch. Int. Med. **94**:925, 1954.
101. Metcoff, J., James, J. A., Gordillo, G., and Antonowincz, I.: Renal electrolyte transport in normal and nephrotic children. Effects of simultaneous infusion of carbonic-anhydrase inhibitor and nonreabsorbable anion, J. Lab. & Clin. Med. **46**:333, 1955.
102. Metcoff, J., Kelsey, W. M., and Janeway, C. A.: The nephrotic syndrome in children. An interpretation of its clinical, biochemical and renal hemodynamic features as variations of a single type of nephron disease, J. Clin. Invest. **30**:471, 1951.
103. Metcoff, J., Nakasone, N., and Rance, C. P.: On the role of the kidney during nephrotic edema: potassium excretion and sodium retention, J. Clin. Invest. **33**:665, 1954.
104. Milne, M. D.: Diseases of the kidney and genitourinary tract. *In* Thompson, R.H.S., and King, E. J.: Biochemical disorders in human disease, New York, 1957, Academic Press, pp. 117-241.
105. Movat, H. Z.: The fine structure of the glomerulus in amyloidosis, A.M.A. Arch. Path. **69**:322, 1960.
106. Movat, H. Z., and McGregor, D. D.: The fine structure of the glomerulus in membranous glomerulonephritis (lipoid nephrosis) in adults, Am. J. Clin. Path. **32**:109, 1959.
107. Muehrcke, R. C., Kark, R. M., Pirani, C. L., and Pollack, V. E.: Lupus nephritis: a clinical and pathological study based on renal biopsies, Medicine **36**:1, 1957.
108. Muehrcke, R. C., Pirani, C. L., Pollack, V. E., and Kark, R. M.: Primary renal amyloidosis, with the nephrotic syndrome studied by serial biopsies of the kidney, Guy's Hosp. Rep. **104**:295, 1955.
109. Muerhcke, R. E.: The fingernails in chronic hypoalbuminemia, a new clinical sign, Brit. M. J. **1**:1327, 1956.
110. Munk, F.: Klinische Diagnostik der degenerativen Nierenerkrankungen. I. Sekundar-degenerative primär-degenerative Nierenerkrankung. II. Degenerative Syphilisniere, Ztschr. klin. Med. **78**:1, 1913.
111. Munk, O., and Nissen, N. I.: Development of nephrotic syndrome during treatment with mercurial diuretics, Acta med. scandinav. **153**:307, 1956.
112. Murphy, F. D., and Schulz, E. G.: Natural history of glomerulonephritis, Arch. Int. Med. **98**:783, 1956.
113. Najjar, V. A., and Fisher, J.: Mechanism of antibody-antigen reaction, Science **122**:1272, 1955.
114. Philips, I., Calvin, J. K., and Kagan, B. M.: Nephrotic syndrome in children: observations on clinical course and influence of sulphonamide and antibiotic therapy, A.M.A. J. Dis. Child **85**:451, 1953.
115. Piel, C. F., Dong, L., Modern, M. O., Goodman, J. R., and Moore, R.: The glomerulus in experimental renal disease in rats as observed by light and electron microscopy, J. Exper. Med. **102**:573, 1955.
116. Piel, C. F., and Williams, G. F.: Long-continued adrenal hormone therapy in childhood nephrosis, J. Am. M. Women's A. **12**:273, 1957.
117. Platt, R., Stewart, A. E., and Emery, E. W.: The aetiology, incidence and heredity of pre-eclamptic toxemia of pregnancy, Lancet **1**:552, 1958.
118. Pollack, V. E., Kark, R. M., Pirani, C. L., Shafter, H. A., and Muehrcke, R. C.: Renal vein thrombosis and the nephrotic syndrome, Am. J. Med. **21**:496, 1956.
119. Pollack, V. E., Pirani, C. L., Kark, R. M., Muehrcke, R. C., Freda, V. C., and Nettles, J. B.: Reversible glomerular lesions in toxemia of pregnancy, Lancet **2**:59, 1956.
120. Pollack, V. E., Pirani, C. L., Muehrcke, R. C., Pulos, P. C., Kark, R. M., and Steck, I. E.: On renal involvement in systemic lupus erythematosus and other so-called collagen diseases, Arthritis. Rheum. **1**:204, 1958.
121. Post, R. S., and Eckel, R. E.: Hormone therapy of the adult nephrotic syndrome of unknown etiology, J. Chron. Dis. **12**:211, 1960.
122. Proceedings of the Sixth Annual Conference on the Nephrotic Syndrome (J. Metcoff, editor), National Nephrosis Foundation, Inc., 1955, p. 189.
123. Proceedings of the Eighth Annual Conference on the Nephrotic Syndrome (J. Metcoff, editor), National Nephrosis Foundation, Inc., 1957, p. 22.
124. Proceedings of the Ninth Annual Conference on the Nephrotic Syndrome (J. Metcoff, editor), National Nephrosis Foundation, Inc., 1958.
    a. Gitlin, Baxter, Rodbell, Gordon, Bally, pp. 82-147.
    b. Lange, et al., pp. 13-39
    c. Goodman et al., pp. 61-81.
125. Proceedings of the Tenth Annual Conference on the Nephrotic Syndrome (J. Metcoff, editor), The National Kidney Disease Foundation, 1959.
    a. Kark, p. 215.
    b. Lange, p. 211.
    c. Heymann, p. 177.
    d. Arneil, p. 249.
    e. Vernier, p. 66.
    f. Ellis, p. 87.
    g. Heymann, p. 172.
    h. Lange, p. 237.
    i. Lange, p. 244.
    j. Lange, p. 278.
    k. Riley, p. 273.
    l. Farquhar, p. 2.
126. Protein-losing gastroenteropathy (editorial), Lancet **1**:351, 1959.
127. Ravdin, I. S.: Plasma expanders, J.A.M.A. **150**:10, 1952.
128. Recant, L.: Abnormality in thyroxine binding in nephrosis, (abstract) J. Clin. Invest. **35**:730, 1956.
129. Recant, L., Borowsky, B., and Dubach, U.: Aminonucleoside glomerulonephritis in rats, Proceedings of the 41st Annual Session of the

American College of Physicians, 1960, p. 113.

130. Reed, R. W., and Mathison, B. H.: Experimental nephritis due to type-specific streptococci. I. The effect of a single exposure to type-12 streptococci, J. Infect. Dis. **95**:191, 1954.
131. Reid, R. T. W.: Electron microscopy of glomeruli in nephrotoxic serum nephritis, Australian J. Exper. Biol. & M. Sc. **34**:143, 1956.
132. Robbins, J., Rall, J. E., and Petermann, M. L.: Thyroxine-binding by serum and urine proteins in nephrosis: qualitative aspects, J. Clin. Invest. **36**:1333, 1957.
133. Rosenman, R. H., Friedman, M., and Byers, S. O.: The causal role of plasma albumin deficiency in experimental nephrotic hyperlipemia and hypercholesterolemia, J. Clin. Invest. **35**:522, 1956.
134. Roscoe, M. H.: The nephrotic syndrome, Quart, J. Med. **25**:353, 1957.
135. Rowe, D. S.: The similarity of the protein mixtures derived from serum by selective ultrafiltration to the urine proteins in the nephrotic syndrome, J. Physiol **135**: 1-2P, 1956.
136. Rytand, D. A.: Onset of the nephrotic syndrome during reaction to bee sting, Stanford M. Bull. **13**:224, 1955.
137. Rytand, D. A.: Fatal anuria, nephrotic syndrome and glomerular nephritis as sequels of dermatitis of poison oak, Am. J. Med. **5**:548, 1948.
138. Rytand, D., and Cox, A. J., Jr.: Polycyclic nephrotic syndrome, Am. J. Med. **22**:297, 1957.
139. Schreiner, G. E.: 3-D for diagnosis, G.P. **9**:70, 1954.
140. Schreiner, G. E.: Some observations on telescoped urinary sediments, Ann. Int. Med. **42**:826, 1955.
141. Schreiner, G. E., and Berman, L. B.: Experience with 150 consecutive renal biopsies, South. M.J. **50**:733, 1957.
142. Schwartz, M., and Thomsen, B.: Idiopathic or hypercatabolic hypoproteinemia—case examined by I^{131}-labeled albumin, Brit. M. J. **1**:14, 1957.
143. Seegal, B. C., and Bevans, M.: The production of glomerulonephritis by immunologic methods, J. Chron. Dis. **5**:153, 1957.
144. Sellers, A. L.: Unpublished observations. Quoted by Adams, D. A.: The pathophysiology of the nephrotic syndrome, A.M.A. Arch. Int. Med. **106**:117, 1960.
145. Shreeve, W. W., Hutchin, M. E., Harper, H. A., Miller, C. D., and Doolan, P. D.: Excretion of amino-acids in nephrosis, Proc. Soc. Exper. Biol. & Med. **88**:510, 1955.
146. Spargo, B., McCartney, C. P., and Winemiller, R.: Glomerular capillary endotheliosis in toxemia of pregnancy, Arch. Path. **68**:593, 1959.
147. Spiro, D.: The structural basis of proteinuria in man. Electron microscopic studies of renal biopsy specimens from patients with lipid nephrosis, amyloidosis, subacute and chronic glomerulonephritis, Am. J. Path. **35**:47, 1959.
148. Steiger, W. A., Zarafonetis, C. J. D., Miller, G. M., Seifter, J., and Baeder, D. H.: Preliminary report on the effects of a plasma lipid mobilizing factor in man, Am. J. M. Sc. **232**:605, 1956.
149. Sterling, K.: The turnover rate of serum albumin in man as measured by I^{131}-tagged albumin, J. Clin. Invest. **30**:1228, 1951.
150. Squire, J. B.: The nephrotic syndrome, Advances Int. Med. **7**:201, 1955.
151. Squire, J. R., Blainey, J. D., and Hardwicke, J.: The nephrotic syndrome, Brit. M. Bull. **13**:43, 1957.
152. Taylor, R. D., Corcoran, A. C., and Page, I. H.: Treatment of the nephrotic syndrome with nitrogen mustard, J. Lab. & Clin. Med. **36**:996, 1950.
153. Ulstrom, R. A., Smith, N. J., and Meimlich, E. M.: Transient dysproteinemia in infants, a new syndrome, A.M.A. J. Dis. Child. **92**:219, 1956.
154. Vernier, R. L., Brunson, J., and Good, R. A.: Studies on familial nephrosis. I. Clinical and pathologic study of four cases in a single family, A.M.A. J. Dis. Child. **93**:469, 1957.
155. Wachstein, M., and Lange, K.: Proteinuria and tubular atrophy in the rat. Their relationship as studied by enzymatic histochemistry, with special reference to the antirabbit-kidney serum nephritis and aminonucleoside nephrosis, Lab. Invest. **9**:371, 1960.
156. Wilson, V. K., Thomson, M. L., and Holzel, A.: Mercury nephrosis in young children, with special reference to teething powders containing mercury, Brit. M. J. **1**:358, 1952.
157. Woolf, L. I., and Giles, H. McC.: Urinary excretion of amino-acids and sugar in the nephrotic syndrome. A chromatographic study, Acta paediat. **45**:489, 1956.
158. Worthen, H. G., Vernier, R. L., and Good, R. A.: The syndrome of infantile nephrosis, (abstract) A.M.A. J. Dis. Child **96**:585, 1958.
159. Wren, J. C., and Nutt, R. L.: Nephrotic syndrome occurring during paramethadione therapy, J.A.M.A. **153**:918, 1953.

Annotations

The preservation of myocardial function during open-heart surgery

In the final analysis the success or failure of an intracardiac operation will largely depend on the adequacy of the reconstructive procedure, the extent of secondary changes in other organs, such as the pulmonary vascular bed, and the degree to which the contractile force and energy reserves of the myocardium have been conserved. When severe pulmonary hypertension, congestive heart failure, or advanced myocardial hypertrophy are present, the last group of factors assume critical importance, because the relationship between myocardial reserves and the obligatory work load demanded of the heart in the postoperative period may be in a fine state of balance.

The clinical adoption of many features of current surgical practice has preceded proper evaluation of their effects on myocardial function. Total body perfusion, even when prolonged for 2 hours, has no detectable effect on ventricular function. Incision of the ventricle, on the other hand, invariably results in immediate impairment of function, the degree of impairment being related to the length and site of the incision.[1] The late effects of ventriculotomy are virtually unknown and constitute an important field for further study.

Hypothermia is frequently induced during total body perfusion. From the evidence available[2] it would appear that moderate hypothermia has no immediate effects on ventricular function, but, clearly, deep hypothermia has[3]; the heart frequently fails as the temperature is reduced below 25°C. It is presumed, but quite unproved, that these effects are completely reversed on rewarming. The histologic changes which follow hypothermia, demonstrated by Sarajas, Senning and Kaplan,[4] probably have functional accompaniments.

The deliberate induction of asystole by the Melrose technique has been shown by a number of workers[5-7] to result in lasting impairment of function and should probably be discarded as being more harmful than simple anoxic arrest. Hypothermia appears to lessen the damage done by the use both of potassium citrate[8] and of prolonged anoxic arrest.[9] The consensus of opinion is that, whereas simple anoxic arrest is better tolerated than potassium-induced asystole, anoxic arrest for 20 minutes results in significant reductions in ventricular function. Interrupted aortic occlusion, allowing coronary circulation briefly after each 5 minutes of cardiac anoxia, appears to conserve ventricular function better than any of the other techniques which have been advocated.[5,7] Some further latitude may be provided for the surgeon if interrupted aortic occlusion is combined with moderate hypothermia.

Whatever the technique of inducing asytole, the paramount importance of avoiding passive distention of either the right or left side of the heart, by adequate decompression, is now well recognized. It is similarly apparent to those working in the field that the heart takes at least a few minutes to recover even partially from any insult, be it anoxic or chemical. It is advisable, therefore, to continue total bypass for at least 5 minutes after the release of the aortic clamp, and to submit the heart gradually to its full work load after a further period of partial bypass.

Even the anesthetic agents we use have significant effects on ventricular function, but these are probably completely reversible. Halothane, which has much to commend it as an anesthetic agent in cardiac surgery, has quite a marked depressant effect on cardiac contractility in the concentrations which are used in clinical practice.[10] Further study of other agents is necessary.

It is clearly impossible in a short review to gain an adequate perspective of the various factors which have been mentioned. It is probable that these effects are additive and summate maximally in the period immediately after bypass. Although some are clearly reversible, our knowledge of the late effects of ventriculotomy, deep hypothermia, and induced asystole is quite fragmentary and awaits further elucidation.

Surgery is both an art and a science, and judgment is often the final arbiter. A sound knowledge of the functional effects of the techniques we use should help us to make the best compromise in each case between the often conflicting interests involved in, on the one hand, conserving the function of the myocardium and, on the other, providing ideal conditions for surgical repair.

The compromise reached will necessarily vary from case to case. In operations on patients in the older age group or on patients who have been in failure or who have gross ventricular hypertrophy, it can be presumed that the myocardial reserves are low, and surgical technique should be designed around the concept of maximally conserving these reserves. In some younger patients without these

accompaniments it is perhaps justifiable to take a calculated risk in order to provide better access so that complete repair of the defect is ensured. There can be no substitute in these matters for mature surgical judgment based on an adequately studied past experience.

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REFERENCES

1. Stirling, G. R., Stanley, P. H., and Lillehei, C. W.: The effects of cardiac bypass and ventriculotomy upon right ventricular function; with report of successful closure of ventricular septal defect by antriotomy, S. Forum **8**:433, 1958.
2. McMillan, I. K. R., Case, R. B., Stainsby, W. W., and Welch, G. H.: The hypothermic heart; work potential and coronary flow, Thorax **12**:208, 1957.
3. Drew, C. E., Keen, G., and Benazon, D. B.: Profound hypothermia, Lancet **1**:745, 1959.
4. Sarajas, H. S. S., Senning, A., and Kaplan, J.: Heart damage in dogs subjected to hypothermia, circulatory arrest and cardiac surgery, Am. Heart J. **52**:836, 1956.
5. Braunwald, N. S., Waldhausen, J. A., and Cornell, W. P.: Left ventricular function following elective cardiac arrest, Circulation **20**:676, 1959.
6. Weirich, W. L., Jones, R. W., and Burke, M. F.: The effect of elective cardiac arrest induced by potassium citrate and acetylcholine on ventricular function, S. Forum **10**:528, 1960.
7. Stirling, G. R., Morris, K. N., and Race, D.: The effect of induced asystole on ventricular function, Australia & New Zealand J. Surg., 1960. (In press.)
8. Cooper, T., William, V. L., Zafiracopoulos, P., and Hanlon, C. R.: Myocardial function after elective cardiac arrest during hypothermia, Surg., Gynaec. & Obst. **109**:423, 1959.
9. Shumway, N. E., Lower, R. R., and Stofer, R. C.: Selective hypothermia of the heart in anoxic cardiac arrest, Surg. Gynec. & Obst. **109**:750, 1959.
10. Stirling, G. R., Morris, K. N., Orton, R. H., Boake, W. C., Race, D., Kinross, F., Thompson, J. W., and Crosby, W.: Halothane and circulatory occlusion; some experimental and clinical observations, Brit. J. Anaesth. **32**:262, 1960.

Ultrasonic cardiography

The method, inaugurated by Edler and Hertz,[1,2] in 1954, at the University of Lund, Sweden, has been introduced at the I. Medical Department in Düsseldorf[4,5] and at some other medical clinics in Germany[8,9] as a routine procedure in order to estimate the degree of mitral stenosis. The physical principle is generally known: the registration of ultrasonic echo, which originates from borderlines of different media. If sonic energy is sent through the human heart, a partial sonic reflection—in this case an ultrasonic echo—will arise at the border between cardiac walls and the surrounding tissue, that is, between the cardiac walls and the blood.

For the generation of ultrasonic energy and the simultaneous receiving of the reflected sonic energy a piezoelectric electroacoustic transducer is used (sound-frequency 1-2.5 megacycles). The sound radiation is not a continuous but a periodic one (the duration of impulse is 1 to 7 μsec.). The reflected sound impulse is reconducted to the piezoelectric quartz, which in the meantime has been switched onto reception. For visualization a cathoderay oscillograph is used after amplification. The instrument used is a commercially available ultrasonic impulse set which has been developed for the testing of materials.

If the reflecting cardiac wall is moved toward the ultrasonic transmitter, the echos on the fluorescent screen will move toward the X-axis. This movement is a time-function curve. Through the use of a transmitting frequency of 200 impulses per second it is possible to register the movement of special cardiac walls with an accuracy of measurements of 5 microseconds.

If in the human subject the ultrasonic transmitter is placed over the third intercostal area on the left parasternal side, a moving curve is recorded which shows the characteristic forms of a venous curve with two maxima at the time of atrial systole, and having at the refilling phase a minimum at the time of ventricular systole. In case of incomplete or complete atrioventricular block the first maximum constantly appears 0.07 second after the beginning of the P wave in the ECG. This maximum is absent in case of atrial fibrillation. In case of atrial flutter, mechanical flutter waves may be registered.[5]

In mitral stenosis the second maximum is recorded synchronously with the mitral opening snap in the phonocardiogram. The following part of the curve, which corresponds to the time of ventricular filling, that is, the atrial depletion after the opening of the mitral valve, progresses the plainer the greater the degree of mitral stenosis. In other words, the registered part of the heart will move more slowly from the chest wall the greater the degree of mitral stenosis. The closeness of the quantitative correlations to the anatomic condition, which is in accordance with the opening area of

the mitral valve, has been investigated in the meantime on more than 1,500 patients with mitral valvular disease.[5]

It is still unknown at which part of the cardiac wall the sound reflection takes place. By the direction of the sound beam and the special topography, by the form of the curve in respect to the influence of arrhythmia or the synchronous registration of atrial pressure curves or the characteristic forms of the curve in case of mitral stenosis, one can presume that the movement of the anterior wall of the left atrium is registered. The recent investigations of Edler[3] on dead hearts suggest that the movements of the mitral valve itself are recorded.

Since the ultrasonic waves can penetrate the cardiac walls—in contrast to kymography—tumors of the left atrium which may imitate mitral stenosis and large thrombus will give typical ultrasonic echo curves.[6] In the case of hydropericardium the movement of the anterior wall of the left ventricle can be recorded, and, from the distance of the sound generator to the anterior cardiac wall, the amount of effusion can be estimated. If the sound generator is applied over the second intercostal area on the left parasternal side, the moving curve of the A. pulmonalis can be registered.

If the third intercostal area is chosen, using a medial and dorsal direction of the sound beam, the movement of the aortic valve in the human heart in situ can be recorded (Edler, 1960). Probably by this means the distinction between valvular and subvalvular aortic stenosis is possible. But in contrast to mitral valvular disease, in this case there are still some technical difficulties of recording. Practical application to diagnostic procedure in the case of aortic valvular disease cannot yet be considered.

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REFERENCES

1. Edler, J., and Hertz, C. H.: Kungl. Fysiogr. Sällskapets in Lund förhandlingar **24**:Nr. 5, 1954.
2. Edler, J., and Gustafson, A.: Acta med. scandinav. **85**:154, 1957.
3. Edler, J., Gustafson, A., Karlefors, T., and Christensson, B.: III Europäischer Kardiologenkongress, Rome, 1960.
4. Effert, S., Erkens, H., and Grosse-Brockhoff, F.: German M. Month. **2**:325, 1957.
5. Effert, S.: Arch. Kreislaufforsch. **30**:213, 1959.
6. Effert, S., and Domanig, E.: German M. Month. **4**:1, 1959.
7. Effert, S., Hertz, C. H., and Böhme, W.: Ztschr. Kreislaufforsch. **48**:230, 1959.
8. Gässler, E., and Samlert, H.: Ztschr. Kreislaufforsch. **47**:291, 1958.
9. Schmitt, W., and Braun, H.: Ztschr. Kreislaufforsch. **49**:214, 1960.

The electrocardiogram in pulmonary emphysema and chronic cor pulmonale

The electrocardiographic changes which occur in pulmonary emphysema and in chronic cor pulmonale have been well described.[1-7] Although some definitions of chronic cor pulmonale include a wide variety of conditions with right heart failure secondary to pulmonary hypertension, we shall use the term chronic cor pulmonale in its restricted sense of that of right heart disease secondary to pulmonary emphysema.

The electrocardiographic patterns which have been described in pulmonary emphysema and chronic cor pulmonale include the following: (1) $\hat{A}P$ (frontal mean P wave axis) $> +60°$ to $+90°$ resulting in tall peaked P waves in Leads II, III and aV_F, often accompanied by prominent T_a waves; (2) $\hat{A}QRS$ (frontal mean QRS axis) $+90°$ or greater (right axis deviation, vertical heart); (3) transition zone displaced to the left ("clockwise rotation"), with RS pattern in left precordial leads; (4) negative, or predominantly negative, QRS complexes (rS, QS) in all precordial leads; (5) low voltage QRS in limb and/or left precordial leads; (6) S_1, Q_3 pattern; (7) S_1, S_2, S_3 syndrome; (8) T-wave inversion in right precordial leads; (9) abnormal left axis deviation; (10) classic right ventricular hypertrophy (RVH) in Lead V_1 (V_{3R}) with dominant R wave (Rs, R, qR, QR, qRs); (11) rSR′ in Lead V_1 (V_{3R}); (12) complete right bundle branch block; (13) normal or nonspecific tracing.

The distinction between the electrocardiographic changes that may be produced by emphysema alone and those that are due to associated right ventricular hypertrophy is at times difficult. To attempt to make such a distinction, however, is important since changes in the electrocardiogram may be, occasionally, the earliest objective manifestation of cor pulmonale. Conversely, the effect of pulmonary emphysema alone on the electrocardiogram should not be misdiagnosed as that of right ventricular hypertrophy. It will be best to consider the effect of each of these factors separately.

Milder degrees of pulmonary emphysema may have no recognizable effect on the electrocardiogram. More severe degrees of emphysema (as measured by pulmonary function tests), however, may bring about certain characteristic changes in the electrocardiogram.[7]

The heart becomes vertically placed because of the low diaphragmatic position. This results in a vertical electrical position of the heart and a rightward deviation of the mean QRS and P-wave axes in the frontal plane. Because of the low-lying position of the heart, the customary precordial lead positions will be high, and most, or all, of the six leads may lie in the area of relative negativity for the mean QRS vector and record predominantly negative QRS deflections from Leads V_1-V_6 (rS or QS). If the heart is not displaced quite so low in the chest, the null plane of the mean QRS vector may be relatively parallel to the six precordial leads, and these will display a transitional type of complex (RS) even as far to the left as Lead V_6. Posterior rotation of the mean QRS vector in the horizontal plane also contributes to the shift of the transition zone to the left ("marked clockwise rotation").[8,9] When the heart assumes a vertical position, there tends to be clockwise rotation on the longitudinal axis of the QRS electrical field (not to be confused with anatomic rotation of the heart, for which there is little evidence[10]), with the appearance of an S_1 and a Q_3. The QRS voltage is low because (1) the electrodes are relatively far removed from the ventricles; (2) the emphysematous lung is a poor electrical conductor; (3) the spatial QRS vector tends to be posteriorly directed, with a resultant small projection on the frontal plane.

It is thus readily apparent that emphysema alone may produce virtually any of the electrocardiographic patterns that have been enumerated, except perhaps the more classic ones of RVH in the right precordial leads, the more marked degrees of right axis deviation (> + 110°), and right ventricular conduction defects. The issue is further complicated by the fact that even advanced cor pulmonale with considerable anatomic RVH only rather uncommonly results in high voltage in the right precordial leads and, in fact, may exhibit no electrocardiographic evidence of RVH.[11] Right ventricular conduction defects are suggestive, but certainly not diagnostic, of right ventricular enlargement in cases of pulmonary emphysema.[3,12]

The classic "P-pulmonale" pattern may occur with emphysema alone or may be the sole electrocardiographic manifestation of anatomically proved cor pulmonale.[11] Some authors[2a,7] believe that these P-wave changes are not caused by vertical position alone but may result from right atrial enlargement (dilatation and/or hypertrophy).

The abnormal left axis deviation (in the range of −90°) occasionally encountered in severe pulmonary emphysema has been ascribed to abnormal transmission of electrical potentials[10] or to associated left ventricular enlargement or conduction disturbance,[13] or, in fact, is actually marked right axis deviation.[7,8] Another proposed explanation is the "axis-illusion" phenomenon[6,13] in which the posteriorly directed mean QRS force is nearly perpendicular to the frontal plane, and only a slight superior shift in this vector in the sagittal plane will project it on the frontal plane as a markedly superiorly directed force.

Abnormal QRS patterns (qR, QS) suggestive of anteroseptal, anterior, and anterolateral myocardial infarction have been well documented in cases of chronic cor pulmonale,[4,14] and have been attributed to right ventricular dilatation with or without RVH[14] as well as to the posterior orientation of the mean QRS axis.[8,9] Abnormal Q waves in Leads II, III, and aV_F simulating inferior myocardial infarction have also been described occasionally in chronic cor pulmonale.[4,6,8]

Arrhythmias, other than sinus tachycardia, are uncommon in chronic cor pulmonale but may occur.[13]

It has been demonstrated in patients with chronic cor pulmonale that if the electrocardiographic pattern of RVH is present, the mean pulmonary arterial pressure usually exceeds 30 mm. Hg,[12] and those patients with chronic cor pulmonale whose total pulmonary vascular resistance exceeds 750 dynes seconds cm.$^{-5}$ exhibit either RVH or a right ventricular conduction defect. It should be noted, however, that not all patients whose mean pulmonary arterial pressure exceeds 30 mm. Hg display electrocardiographic RVH. It has also been observed that those patients with chronic cor pulmonale who have hypoxia (arterial oxygen saturation < 85 per cent) commonly show RVH in the electrocardiogram.[12]

In conclusion, it may be stated that the electrocardiographic differentiation of cases of pulmonary emphysema without cor pulmonale from cases with cor pulmonale is often difficult or impossible. However, when the classic electrocardiographic pattern of RVH appears, it usually indicates an advanced state of the disease, generally associated with pulmonary hypertension and hypoxia.[3,12]

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REFERENCES

1. Zuckermann, R., Cabrera, E., Fishleder, B. L., and Sodi-Pallares, D.: Electrocardiogram in chronic cor pulmonale, AM. HEART J. **35**:42, 1948.
2a. Wood, P.: Electrocardiographic appearance in acute and chronic pulmonary heart disease, Brit. Heart J. **10**:87, 1948.
2b. Wood, P.: Diseases of the heart and circulation, ed. 2, Philadelphia, 1956, J. B. Lippincott Company.
3. Mounsey, J. P. D., Ritzmann, L. W., and Selverstone, N. J.: Cardiographic studies in severe pulmonary emphysema, Brit. Heart J. **14**:442, 1952.
4. Sodi-Pallares, D., and Calder, R. M.: New bases of electrocardiography, St. Louis, 1956, The C. V. Mosby Company.
5. Bremer, E. M., and Hellmuth, G. A.: The electrocardiographic diagnosis of chronic cor pulmonale, Tr. Am. Coll. Cardiol. **7**:120, 1957.
6. Littmann, D.: The electrocardiographic findings in pulmonary emphysema, Am. J. Cardiol. **5**:339, 1960.
7. Wasserburger, R. H., Kelly, J. R., Rasmussen, H. K., and Juhl, J. H.: The electrocardiographic pentalogy of pulmonary emphysema, Circulation **20**:831, 1959.
8. Massie, E., and Walsh, T. J.: Clinical vectorcardiography and electrocardiography, Chicago, 1960, The Year Book Publishers, Inc.

9. Walsh, T. J., Roman, G. T., Jr., and Massie, E.: The vectorcardiographic QRSsÊ-loop findings in chronic cor pulmonale, Am. Heart J. **60**:592, 1960.
10. Grant, R. P.: Clinical electrocardiography. The spatial vector approach, New York, 1957, McGraw-Hill Book Company, Inc.
11. Phillips, R. W.: The electrocardiogram in cor pulmonale secondary to pulmonary emphysema: a study of 18 cases proved at autopsy, Am. Heart J. **56**:352, 1958.
12. Scott, R. C., Kaplan, S., Fowler, N. O., Helm, R. A., Westcott, R. N., Walker, I. C., and Stiles, W. J.: The electrocardiographic pattern of right ventricular hypertrophy in chronic cor pulmonale, Circulation **11**:927, 1955.
13. Spodick, D. H.: Electrocardiographic studies in pulmonary disease. I. Electrocardiographic abnormalities in diffuse lung disease, Circulation **20**:1067, 1960.
14. Myers, G. B.: QRS-T patterns in multiple precordial leads that may be mistaken for myocardial infarction. II. Right ventricular hypertrophy and dilatation, Circulation **1**:860, 1950.
15. Corazza, L. J., and Pastor, B. H.: Cardiac arrhythmias in chronic cor pulmonale, New England J. Med. **259**:862, 1958.

Indicator-dilution techniques in diagnostic cardiology

Stewart[1] first described the dilution principle for measuring blood flow which was subsequently applied to the study of the human circulation by Hamilton and his co-workers.[2] However, the relatively recent work of Wood and his group[3] at the Mayo Clinic has stimulated great interest in the application of the indicator-dilution principle to diagnostic cardiology.

The use of a great number of indicators has been described in a rapidly expanding literature. Colored dyes (methylene blue, Evans blue, indigo carmine, Coomassie blue, and carbocyanine), radioactive liquids and gases (albumin I^{131}, ethyl iodide I^{131}, Kr^{85}), foreign gas (nitrous oxide), radiopaque dyes (Diodrast, Hypaque, Cardiografin), and radioisotope-tagged red blood cells are some of the indicators which have been used in the study of circulation. Although the technique and detecting devices may vary considerably, depending on the indicator employed, the principles underlying their use are common to all. Thus, experience gained with one indicator substance gives an understanding and permits evaluation of results obtained with others.

Excepting the radiopaque dyes used in angiocardiography, the practical choice of indicator lies among the colored dyes, radioactive materials, and foreign gases. In our laboratory, the colored dyes, particularly carbocyanine, have been used with considerable success. The colored dyes yield results comparable to those obtained with radioactive isotopes; they are inexpensive, and their use obviates the need for maintaining a "hot" laboratory—an impracticability for most small institutions.

To be sure, not all colored dyes yield equally satisfactory results. The introduction of carbocyanine by Fox,[4] and Coomassie blue by Taylor and Thorp[5] has provided workers with dyes which do not stain the skin and which permit the recording of dilution curves not distorted by oxygen desaturation. Thus, the chief disadvantages of dyes such as Evans blue have been eliminated.

A good selection of detecting devices, both of the earpiece and cuvette types, is available. In fact, a rugged, stable earpiece transducer can be inexpensively assembled with easily obtainable materials.[6] Such an earpiece has been in continuous use in our laboratory for over a year, without breakdown.

Perhaps the greatest diagnostic usefulness of indicator-dilution techniques is in the detection and localization of central shunts. Although routine cardiac catheterization and blood-oxygen analysis will permit the detection of left-to-right and right-to-left shunts, with the localization of left-to-right shunts, a significant number of such shunts will remain undetected by this method. "False positives" are also not uncommon. Case and associates[7] have pointed out the unreasonably small percentage increase in oxygen content (8-14 per cent) required for the diagnosis of a left-to-right shunt by the oxygen method.

As a rule, moderate and large shunts in either direction or bidirectional shunts can be detected easily by application of indicator-dilution techniques, with a much greater degree of accuracy than the conventional oxygen method. Often, simple inspection of the contour of a dilution curve recorded from the ear after injection of indicator dye into a peripheral vein[8] or the vena cava[9] suffices, and serves as a useful screening procedure. Exact localization of right-to-left shunts is accomplished easily with multiple injections of indicator upstream and downstream from the lesion.

The localization of left-to-right shunts, although more laborious, can be accomplished by any of several satisfactory methods described in the literature. These techniques involve either the use of two catheters in the right heart, double-lumen catheters, or combined left and right heart catheterization.

Approximate quantitation of the magnitude of a shunt is frequently possible by inspection of the recorded indicator-dilution curves. More precise

quantitation may be achieved by measurement of the various parameters of the dilution curve, particularly when the per cent of shunted blood is small.

Intelligent analysis and comparison of dilution curves recorded after the injection of indicator into various locations in the heart and great vessels allows the diagnosis of such lesions as anomalous pulmonary venous drainage, aorticopulmonary window, and transposition of the great vessels, as well as other congenital anomalies.

Indicator-dilution methods have been applied to the study of valvular disease, particularly for the detection and quantitation of regurgitant flow. This application of the dilution principle, because of technical and theoretical considerations, has not been so successful as in the study of central shunts. Nevertheless, useful approximate quantitation of regurgitant flow can usually be made, and results obtained compare more favorably with operative findings than do those obtained with other available methods.

One might question the need for diagnosing and localizing central shunts so small that they are undetected by the conventional oxygen method. If the clinical findings, however, are such that cardiac catheterization is indicated in the first place, then the use of ancillary methods, which introduce no additional hazard to the procedure and allow more accurate diagnosis, is indicated. It is not unlikely that many patients who were considered to have functional murmurs because of normal findings obtained during right heart catheterization would be shown to have small septal defects or other anomalies if restudied with the aid of indicator-dilution techniques. The identification of such lesions and careful follow-up would throw considerable light on the natural history of patients with shunt-type defects and aid in clarifying the indications for surgical intervention.

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REFERENCES

1. Stewart, G. N.: Researches on the circulation time in organs and on the influences which affect it. IV, J. Physiol. **22**:159, 1897.
2. Hamilton, W. F., Moore, J. W., Kinsman, J. M., and Spurling, R. G.: Simultaneous determinations of the pulmonary and systemic circulation times in man and of a figure related to the cardiac output, Am. J. Physiol. **84**:338, 1928.
3. Nicholson, J. W., III, Burchell, H. B., and Wood, E. H.: A method for the continuous recording of Evans blue dye curves in arterial blood, and its application to the diagnosis of cardiovascular abnormalities, J. Lab. & Clin. Med. **37**:353, 1951.
4. Fox, I. J., Brooker, L. S. G., Heseltine, D. W., Essex, H. E., and Wood, E. H.: A tricarbocyanine dye for continuous recording of dilution curves in whole blood independent of variations in blood oxygen saturation, Proc. Staff Meet. Mayo Clin. **32**:478, 1957.
5. Taylor, S. H., and Thorp, J. M.: Properties and biological behavior of Coomassie blue, Brit. Heart J. **21**:482, 1959.
6. Crump, J.: (To be published.)
7. Case, R. B., Hurley, H. W., and Keating, P.: Detection and measurement of circulatory shunts by use of a radioactive gas, Prog. Cardiovas. Dis. **2**:186, 1959.
8. Wiederhielm, C. A., and Bruce, R. A.: Diagnosis of antral shunts from abnormalities of peripheral dye dilution curves, AM. HEART J. **54**:205, 1957.
9. Oakley, C., Taylor, S., Wilcken, D., Hollman, A., Goodwin, J. F., and Shillingford, J.: Dye dilution curves in congenital heart disese, Brit. Heart J. **22**:533, 1960.

Book reviews

DISEASES OF THE NEWBORN. By Alexander J. Schaffer, M.D., Associate Professor of Pediatrics, The Johns Hopkins Medical School, and Pediatrician to the The Johns Hopkins Hospital; formerly, Pediatrician-in-Chief, and, at present, Attending Pediatrician to the Sinai Hospital of Baltimore, Md.; Chief of Pediatrics (Nursery Service), The Hospital for the Women of Maryland. Section on Neonatal Cardiology by Milton Markowitz, M.D., Assistant Professor of Pediatrics, The Johns Hopkins Medical School, and Pediatrician to The Johns Hopkins Hospital; Attending Pediatrician and Director of the Division of Pediatric Cardiology, Sinai Hospital of Baltimore, Md. Philadelphia, 1960, W. B. Saunders Company, 878 pages. Price $20.

The section of this book written by Dr. Markowitz on disorders of the cardiovascular system of the newborn includes chapters on congenital heart disease, myocarditis, cardiac arrhythmias, miscellaneous conditions, and therapy. The introductory chapter contains a good assessment of fetal circulatory changes at birth and of manifestations of heart disease peculiar to the newborn. There is a pattern-type analysis of the electrocardiogram of the newborn, without vector interpretations. The dissertations on myocarditis and arrhythmias will be particularly helpful to physicians concerned with the care of the newborn. Vascular anomalies involving the aortic arch are well presented, with descriptive case histories of congenital stridor in the section on respiratory disorders. Persistent atelectasis in a 7-month-old infant without stridor was found to be caused by constriction of the left main bronchus between a patent ductus arteriosus and an aberrant left pulmonary artery.

Congenital heart disease has become a comprehensive subject and cannot be adequately considered in only the newborn phase of life. Thus, this chapter deals with cardiovascular anomalies as they are encountered in early infancy, and is of necessity abbreviated. A classification with regard to signs and symptoms is given as an aid to differential diagnosis. Emphasis is placed perhaps unduly on the anatomy of defects, with frequent omission of the dynamic and functional effects of different anomalies on the pulmonary and systemic circulations. Catheterization data are not given, thus precluding graphic physiologic interpretations by the reader of clinical signs and radiographic and ECG changes caused by the different anomalies. Discussions of atretic lesions involving the tricuspid, pulmonary, and aortic valves, and transposition of the great vessels are especially appropriate and are well presented in this book. There is a good analysis, with case histories, of anomalous origin of a coronary artery from the pulmonary artery. However, there is no mention of the surgical treatment of this condition, consisting of ligation of the vessel where it joins the pulmonary artery, a procedure proved to be rational by the demonstration of arterialized blood flowing from the anomalous vessel into the pulmonary artery, instead of the reverse type of flow so long presumed.

The liberal use of well-illustrated cases, several furnished to the authors by Dr. Helen Taussig, of Baltimore, helps to make the cardiovascular section of this book interesting and useful to physicians concerned with diagnosis in infants.

CLINICAL VECTORCARDIOGRAPHY AND ELECTROCARDIOGRAPHY. By Edward Massie, A.B., M.D., F.A.C.P., F.A.C.C., Associate Professor of Clinical Medicine, Washington University School of Medicine, St. Louis, Mo.; Director of Heart Stations, Barnes Hospital and Jewish Hospital; Director, Cardiovascular Clinic, Washington University Clinics; Area Consultant in Cardiology, Veterans Administration; and Thomas J. Walsh, B.S., M.D., F.A.C.C., Instructor of Clinical Medicine, Washington University School of Medicine; Associate Director of Heart Station, Barnes Hospital; Visiting Physician, Jewish Hospital; Attending Physician, Washington University Service, Veterans Administration Hospital, St. Louis, Mo. Chicago, 1960, The Year Book Publishers, Inc., 592 pages. Price $27.50.

The stated purpose of this book is to bridge the gap between clinical electrocardiography, vector electrocardiography, and vectorcardiography, and, as might be anticipated, the book is encyclopedic in extent. The best features of the book are the many properly labeled and clear illustrations, and the division of chapters into clinical syndromes, such as cor pulmonale, congenital heart disease, mitral stenosis, and myocardial infarction, with summaries of the abnormal findings at the end of chapters. The chapters dealing with cardiac arrhythmias, drug and electrolyte disturbances, and the W.P.W. syndrome are particularly well done.

There are several undesirable features of the book. The paragraphs describing vectorcardiograms are too verbose. This is caused by the difficulty of describing in print the complicated gyrations of vectorcardiograms. Verbal descriptions of electrocardiograms are awkward, but attempts to describe vectorcardiograms are hopelessly involved and tedious.

Another of the undesirable features concerns the first few chapters. In attempting to review new and basic matters, the authors have got into deep water and consequently have made errors. Fortunately, most of these errors lead only to confusion on the part of the reader, but occasionally the paragraphs have a certain plausibility that could seriously mislead a newcomer to the field. The worst example of this occurs in Chapter 2, wherein Kirchoff's law is badly misstated, after being correctly stated a few pages earlier, and on both occasions has led the author to a wrong general conclusion which would be true only in a special case.

It is regrettable that the authors have dropped the newer concepts of ionic exchange "because of its complexity" in favor of the old Bernstein membrane theory, since the newer ideas, particularly in connection with membrane potential studies, have provided much information in regard to the action of drugs, explanation of injury currents, and the effect of electrolytes. Fortunately, everything the authors have written using Bernstein's theory is equally applicable, or more so, under the newer ideas, so that no serious errors have been made as a result.

Lastly, the reviewer deplores the use of a nonorthogonal lead system to record vectorcardiograms. Although it is true that all vectorcardiograms are interpreted empirically in some degree, this approach will only confuse future studies based on lead systems that are more truly orthogonal. It must be remembered that vectorcardiograms will be truly in the frontal, horizontal, and sagittal planes only if good orthogonal leads are employed.

Lest it seem that the reviewer is overcritical, it might be pointed out that the serious objections to the book apply to a small fraction of it, and actually there is much accurate and useful information, particularly on conventional electrocardiography, in the book.

Announcements

The Life Insurance Medical Research Fund is now receiving applications for two types of awards to be available July 1, 1962, as follows: (1) *Until Oct. 1, 1961,* for postdoctoral research fellowships. Candidates may apply for support in any field of the medical sciences. Preference is given to those who wish to work on fundamental problems, especially those related to cardiovascular function or disease. Minimum stipened is $4,500, with allowances for dependents and necessary travel. (2) *Until Nov. 1, 1961,* for grants to institutions in aid of research on cardiovascular problems. Support is available for physiological, biochemical, and other basic work broadly related to cardiovascular problems, as well as for clinical research in this field.

Further information and application forms may be obtained from the Scientific Director, Life Insurance Medical Research Fund, 1030 East Lancaster Ave., Rosemont, Pa.

The Staff of the Department of Radiology at the University of Rochester regrets that it was not possible to hold the Third Symposium on Cinefluorography in the Spring of 1961, as originally announced. Instead, the meeting will be held in Rochester, New York, on Friday and Saturday, Dec. 1 and 2, 1961. As before, the seating capacity of the auditorium will limit registration to approximately 150 individuals.

The program will include basic orientation in problems of motion picture radiography as well as demonstrations of the applications of cinefluorography in the basic sciences and clinical sciences.

This announcement is an invitation for the submission of scientific papers dealing with any facet of the technical or applied aspects of motion picture radiography.

Address inquiries or applications to: Stanley M. Rogoff, M.D., Division of Diagnostic Radiology, University of Rochester Medical Center, Rochester 20, N. Y.

The Fourth World Congress of Cardiology will be held from Oct. 7 through 13, 1962.

The sessions will be held at the Congress Building which was recently built at the Medical Center in Mexico City. The Congress Building is only a few steps from the Instituto Nacional de Cardiologia and has the best facilities for both scientific sessions and technical exhibits.

The Council on Postgraduate Medical Education of the American College of Chest Physicians will present the following postgraduate courses during 1961: *Cardiopulmonary Problems in Children*, Brown Hotel, Denver, Colo., July 24-28; *Industrial Chest Diseases*, Warwick Hotel, Philadelphia, Pa., Sept. 25-29; *Clinical Cardiopulmonary Physiology*, Sheraton-Chicago Hotel, Chicago, Ill., Oct. 23-27; *Recent Advances in the Diagnosis and Treatment of Heart and Lung Diseases*, Park Sheraton Hotel, New York, N.Y., Nov. 13-17; *Recent Advances in Diseases of the Chest*, Statler-Hilton Hotel, Los Angeles, Calif., Dec. 4-8.

Further information may be obtained by writing the Executive Director, American College of Chest Physicians, 112 East Chestnut Street, Chicago 11, Ill.

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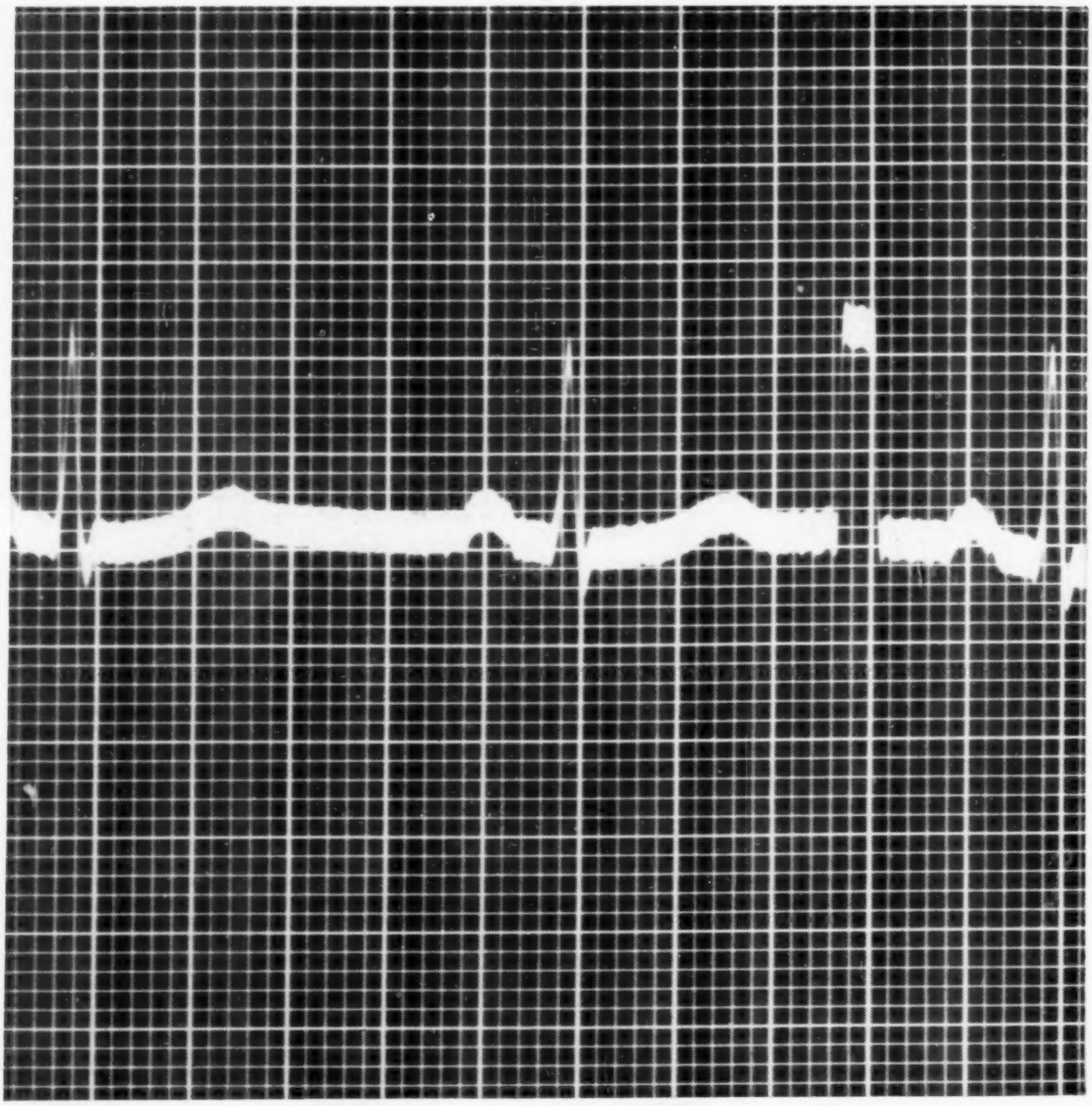

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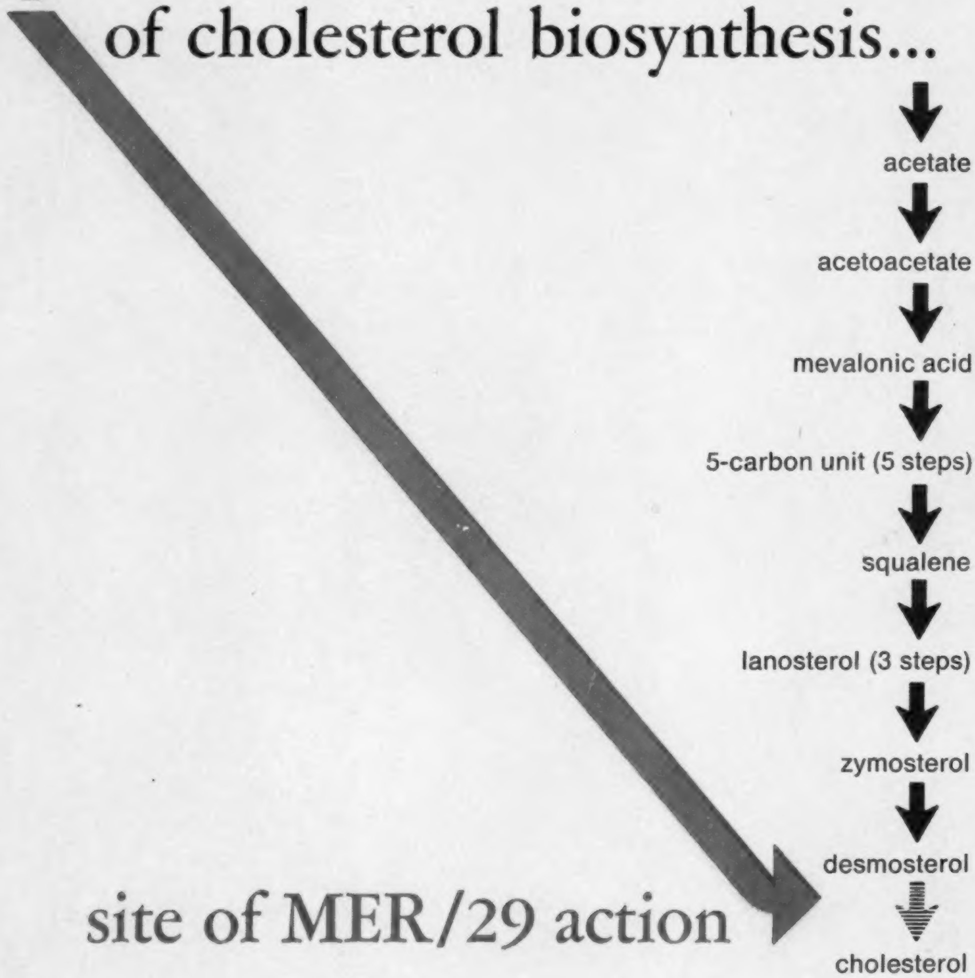

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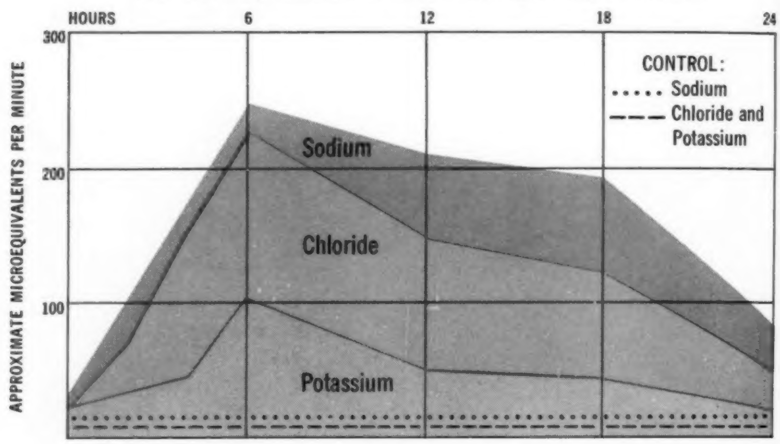

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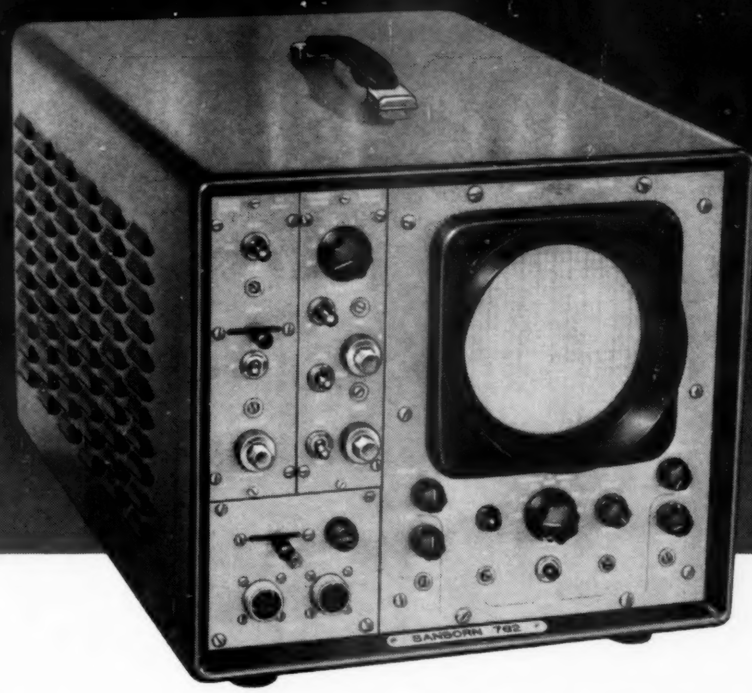

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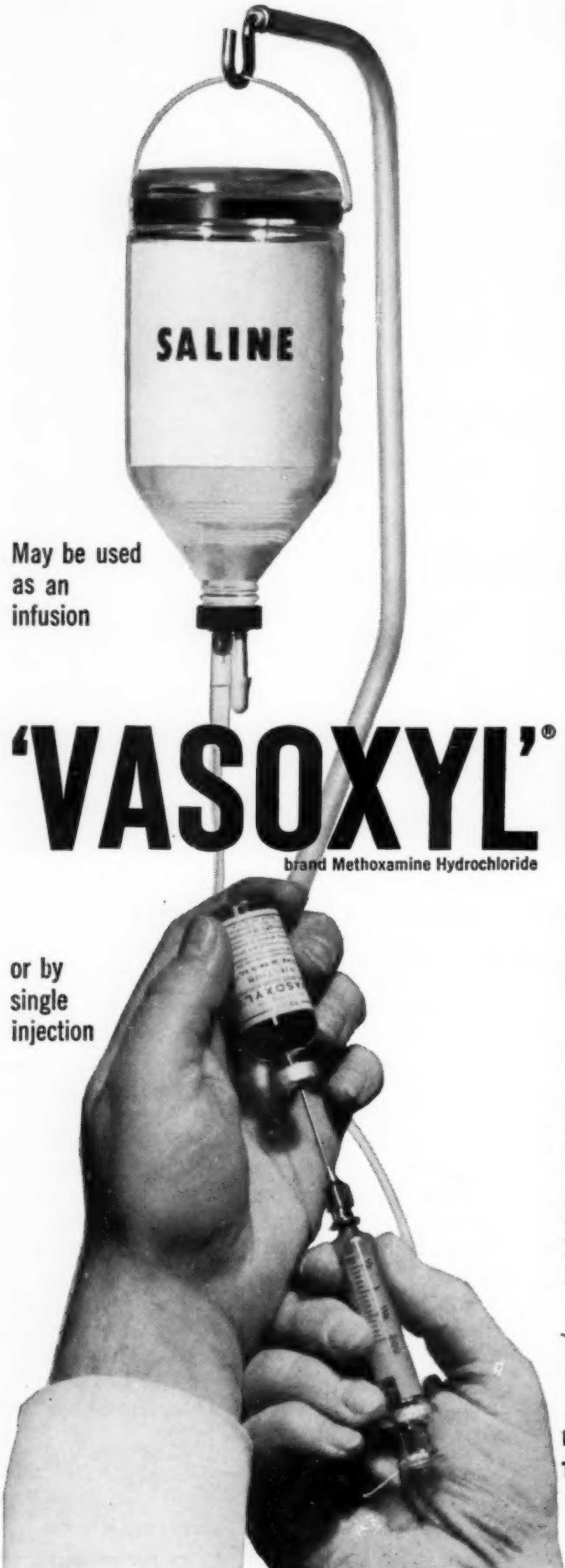

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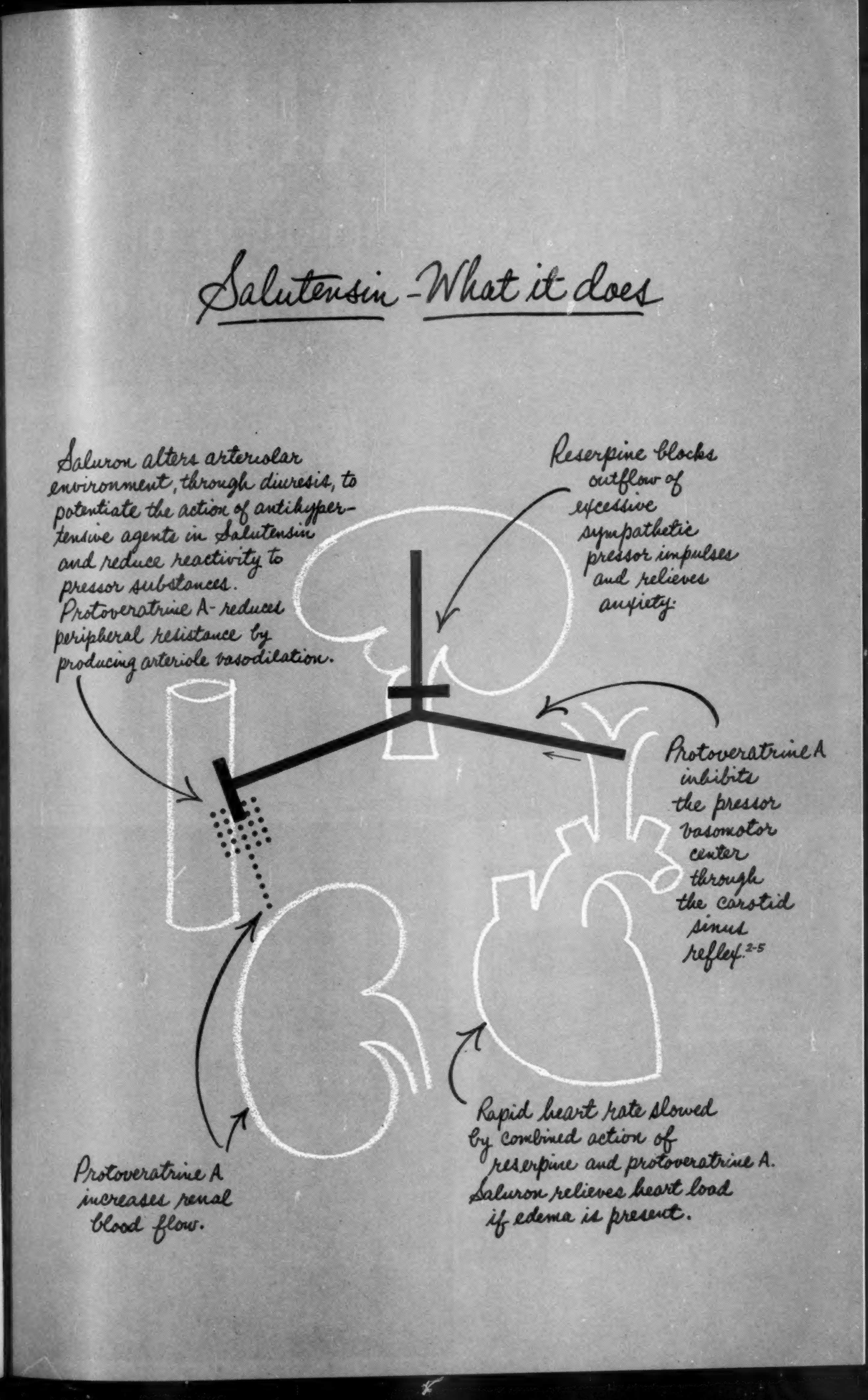
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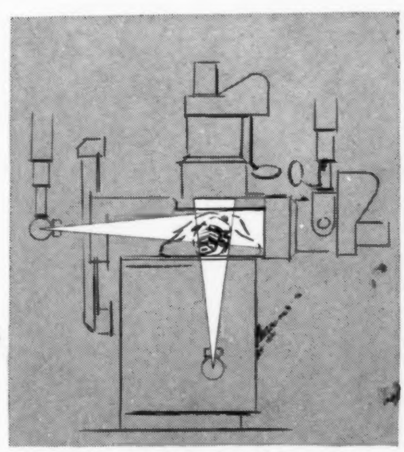

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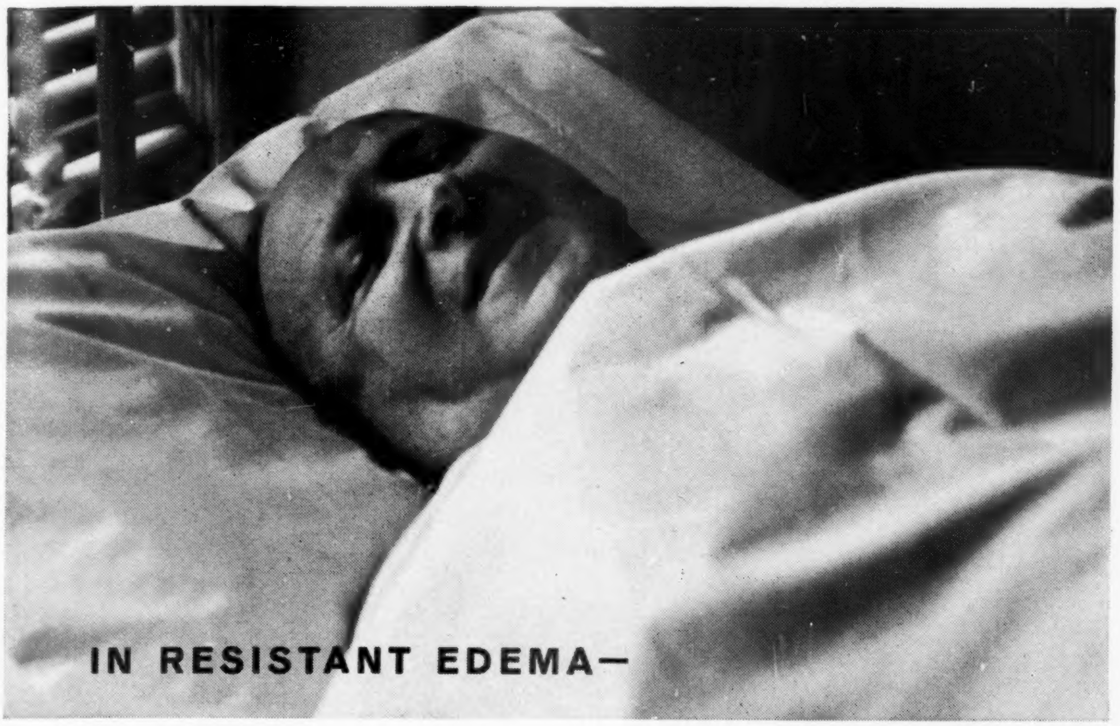

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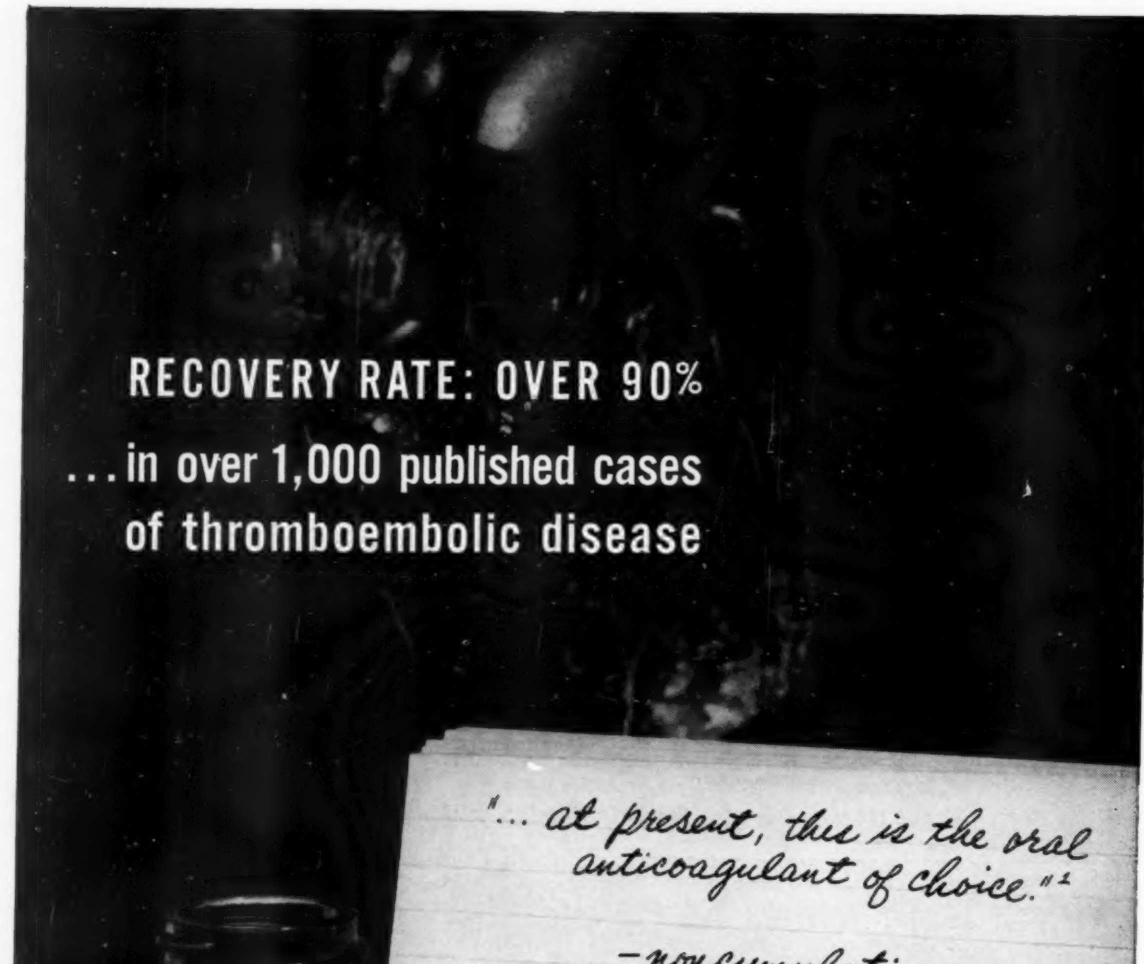

1. Breneman, G. M., and Priest, E. McC.: Am. Heart J. 50:129 (July) 1955. 2. Tandowsky, R. M.: Am. J. Cardiol. 3:551 (April) 1959.

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